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ISOLATED CONGENITAL PULMONARY INCOMPETENCE

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Pulmonary incompetence is common as an acquired lesion. It may follow pulmonary artery dilatation due to pulmonary hypertension or be caused by damage to the valve cusps by surgery, bacterial endocarditis, rheumatic fever or syphilis. As an isolated congenital anomaly, however, it is extremely rare and may be the result of either idiopathic dilatation of the pulmonary artery or congenital abnormalities of the valve cusps. The case to be reported is considered to be another example of the isolated congenital lesion.

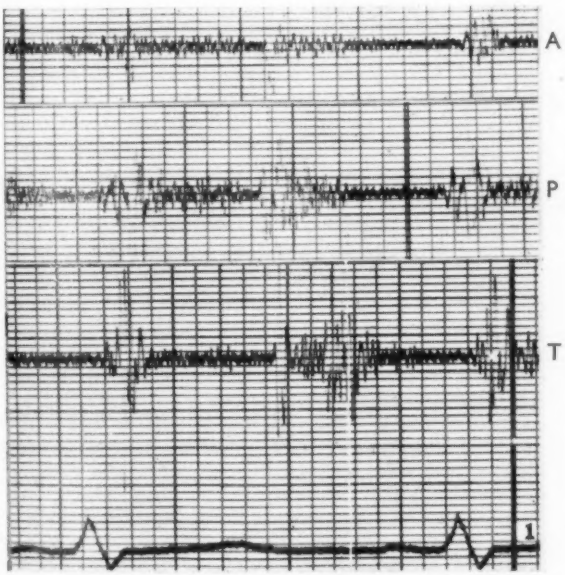

Fig. 1. Phonocardiograms recorded with a Sanborn 'Log' microphone at the aortic (A), pulmonic (P), and tricuspid (T) areas mounted by superimposition of electrocardiograms so that events in the first cycle appear synchronous.

CASE REPORT

A 7-year old boy was admitted to the Cardiac Clinic (Johannesburg General Hospital), for investigation of a cardiac murmur which had been discovered on routine examination some 3 years earlier. He was perfectly well in all respects and had no symptoms. Clinical examination revealed a normally developed young patient; pulse rate 88/min; blood pressure 100/60 mm. Hg; venous pressure normal; no clubbing or cyanosis. The cardiac impulse was unremarkable except for a marked systolic thrust with a short thrill palpable in the pulmonic region. The first heart sound at the mitral area was moderately accentuated where there was a Grade 2 high-pitched blowing systolic murmur. In the pulmonic region the second heart sound was normally split with both components equal. A loud systolic ejection click, a Grade 3 high-pitched pansystolic murmur and a Grade 3 early decrescendo diastolic murmur were also audible. Both these murmurs were conducted down the left sternal border. At the tricuspid area a Grade 2 low-pitched, mid-diastolic murmur was heard (Fig. 1) which became louder with inspiration. The electrocardiogram (Fig. 2) revealed an incomplete right bundle-branch block. Chest X-ray

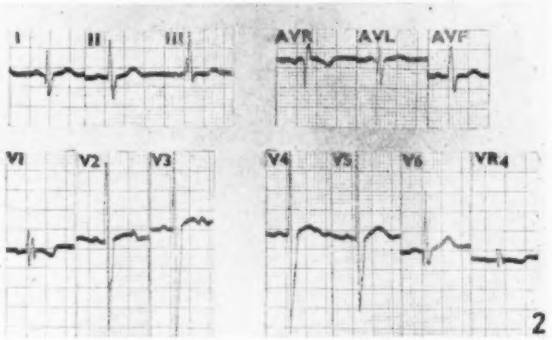

Fig. 2. Electrocardiogram.

Fig. 3. Chest Roentgenogram. Note the full pulmonary arc and normal lung fields.

(Fig. 3) showed a heart of normal size with marked enlargement of the pulmonary artery segment. This vessel showed large pulsations on fluoroscopy and kymography. The lung vascular markings were normal. Cardiac catheterization revealed no evidence of a shunt, with normal pressures in the right atrium (mean 3 mm. Hg) and right ventricles (25/0 mm. Hg). There was a systolic pressure gradient across the pulmonary valve of 10 mm. Hg and an unusually low diastolic pressure (15/5 mm. Hg) (Fig. 4).

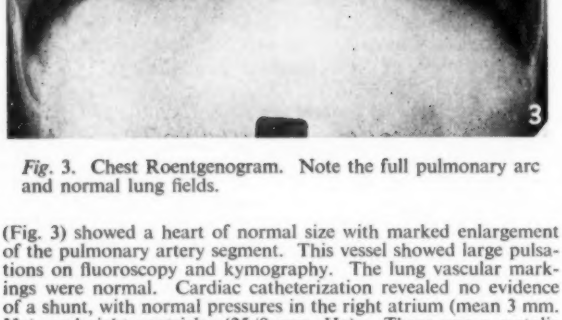

Fig. 4. Pressure record in main pulmonary artery and right ventricle. This is not, as it appears, a continuous withdrawal from artery to ventricle, but is cut from two separate records obtained within the same half minute. Note the negative inflection commencing 0·12 seconds after the onset of the ventricular complex.

Ear oximetry with effort was normal, excluding a significant right-to-left shunt.[1] There was no detectable pressure gradient across the tricuspid valve. An unusual feature of the pulmonary artery pressure curve was the presence of a small negative inflection in early systole producing an apparent delay in the upstroke of the pulmonary pressure curve.

DISCUSSION

The diagnosis of isolated pulmonic regurgitation in this case rests on the following points. There was clinical evidence of pulmonic regurgitation in the form of an early diastolic murmur over and below the pulmonic area without any features of aortic incompetence. This was supported by the presence of a hyperdynamic pulmonary artery segment on screening, and an unusually low pulmonary diastolic pressure with a negative wave in early systole on the pressure record. There was no radiological or catheter evidence of any other lesion which might have caused dilatation of the pulmonary artery. Finally, a congenital origin was supported by the detection of murmurs at an early age. The presence of mild pulmonic stenosis as well cannot be excluded, though it is unlikely in the presence of a normal right ventricular systolic pressure. It seemed more probable that this was an example of functional pulmonic stenosis due either to the marked dilatation of the main pulmonary artery[2] or to increased systolic flow or to both. It is well recognized that a systolic pressure gradient may occur in the absence of organic stenosis in such conditions as anomalous pulmonary venous return or inter-atrial septal defect.[2-5] It has also been observed in artificial pulmonic regurgitation in dogs[6] and in idiopathic dilatation of the pulmonary artery[7].

As an isolated lesion congenital pulmonary incompetence is a rare anomaly. In 1,000 cases of congenital heart disease studied by Abbott[8] there were only 8 cases of primary pulmonary insufficiency, 6 being due to idiopathic dilatation of the pulmonary artery and 2 to cusp abnormalities. Idiopathic dilatation of the pulmonary artery is only associated in a minority of cases with pulmonic regurgitation. For example, in the reports of Green *et al.*,[7] Kaplan *et al.*[9] and Oppenheimer.[10] regurgitation occurred in 8 out of 28 cases and dilatation may have been the cause of the regurgitation in a ninth reported by Morton and Stern.[11] The presence of incompetence due to cusp abnormalities appears to be even less common. Thus Kissin,[12] in a review of 151 case reports of four-cusped pulmonic valves, found evidence of pulmonic incompetence in only 3. Ford and co-workers[13] reviewing the literature of bicuspid pulmonic valve found 16 cases, of whom only 4 may have had an associated pulmonic regurgitation. A case of congenital absence of the pulmonary valve with pulmonic insufficiency and associated with ventricular septal defect has recently been reported by Campeau *et al.*[14]

One cannot be certain whether the regurgitation here was the result of valve deformities or was secondary to dilatation of the pulmonary artery. In those few cases of idiopathic dilatation of the pulmonary artery in which pulmonic regurgitation has been observed, electrocardiograms were normal in all.[4, 7, 9] This suggests that in this condition, incompetence does not reach large proportions. By contrast, incompetence resulting from cusp abnormalities has been associated with 'bundle-branch block' or right ventricular hypertrophy in all cases in which records have been

available.[9, 13, 14] The presence of an incomplete right bundle-branch block pattern in our case therefore, favours its inclusion in the latter group.

The murmur which we have referred to as mid-diastolic appeared earlier in timing than a mitral stenotic murmur and its site of maximal intensity and respiratory variation suggested that it was tricuspid in origin. In the absence of a detectable tricuspid pressure gradient or evidence of increased flow through the tricuspid valve, it seemed possible that this was an 'Austin-Flint murmur' of the tricuspid valve. This implies that it was similar in mechanism to the apical mid-diastolic murmur associated with aortic regurgitation. The murmur described by Ford *et al.*[13] in their case of pulmonic incompetence has a similar configuration.

Of especial interest was the notch which at first glance appeared to occur at the end of diastole (Fig. 4). Comparison with the electrocardiogram indicated, however, that it was early systolic in time. We attributed this negative pressure wave to a Venturi effect produced by an increased stroke volume passing under high velocity into a markedly dilated pulmonary artery. This phenomenon has been observed in pulmonic stenosis[15-17] and has been attributed to a Venturi effect.[15] In pulmonic stenosis it may result in deeply negative inflections in the pressure tracing during systole. For many years a halt in the ascending limb of the pulse in free aortic regurgitation has been recognised and was attributed by Wiggers[18] to sudden acceleration of blood as it enters the aorta. This explanation was offered by Ford *et al.*[13] to explain a similar inflection in the pulmonary artery pressure curve of a subject with pulmonic incompetence, and the same inflection appears in the pulmonary artery pressure record of another case of pulmonary regurgitation reproduced by Kjellberg *et al.*[4] It is in no way diagnostic of pulmonic regurgitation, however, and occurs in a number of congenital anomalies in which pulmonary flow is increased or pulmonary stenosis or pulmonary artery dilatation is present.[19]

Finally, insufficient cases are on record for any reliable information to be available regarding prognosis in this condition. Experimental pulmonary valvectomy in the dog[20] has failed to embarrass the heart significantly and the production of regurgitation following relief of a pulmonic stenosis does not appear to carry a poor prognosis.[21] It is most probable that quite severe degrees of incompetence would be well tolerated in the low-pressure pulmonary circuit.

SUMMARY

Isolated congenital pulmonic regurgitation is a rare condition. A case is reported which had the following characteristics: A pulmonary early diastolic murmur, a mid-diastolic murmur at the tricuspid area, a dilated main pulmonary artery, and an electrocardiogram showing 'incomplete right bundle-branch block'. The pulmonary artery pressure tracing showed a low diastolic pressure, a systolic pressure gradient from right ventricle to pulmonary artery, and a negative notch in the phase of rapid ejection probably due to a Venturi effect. The significance of these features is discussed.

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VAN DIE REDAKSIE

HEMOFILIESE BLOEDING EN DIE BEHANDELING DAARVAN

Bloeding is altyd skrikwekkend, veral as dit nie wil ophou nie, maar by die meeste pasiënte kan dit met betreklik eenvoudige maatreëls beheer word. Dit is egter nie die geval by aangebore bloeiing nie, want hierdie pasiënte hou aan met bloei lank nadat die bloeipunte uitgeken en afgebind is. Onlangse navorsing, wat grootliks in Brittanje gedoen is,[1-3] het egter nuwe lig op die onderwerp van die behandeling gewerp.

Voorbehoeding is natuurlik die eerste noodsaaklikheid, en veel kan gedoen word om besering te voorkom. Bloeiers kneus maklik en met hulle moet 'n mens soos met oorryp tamaties te werk gaan! Seuntjies wat bloeiers is moet nie toegelaat word om mee te doen aan al die aktiwiteite van hul maats nie, hoe graag 'n mens hulle ookal wil toelaat om normale lewes te lei. Gereelde besoeke aan die tandarts kan lastige tandetrek, as die kind ouer is, vermy, en by hierdie pasiënte moet die dokter baie konserwatief in sy houding teenoor snykundige ingreep wees. Slegs die allernoodsaaklikste operasies mag gedoen word. Vandag is die sterftesyfer as gevolg van buikoperasies by bloeiers heel moontlik bo 50 persent in feitlik enige hospitaal in Suid-Afrika. Hierdie syfer is baie groter as die sterftesyfer vir die meeste akute buik-noodgevalle wat sonder operasie met konserwatiewe moderne terapie behandel word; onverligte akute derm-obstruksie is een van die belangrike uitsonderings op hierdie algemene reël. Dan ook word die meeste van die sogenaamde akute buik-noodgevalle by bloeiers veroorsaak deur bloeduitstorting in die derm of die spierwand; gewoonlik kan sulke gevalle ook verlig word sonder snykundige ingreep.

'n Korrekte diagnose van die bloedsiekte is noodsaaklik en dit verg 'n volledige hematologiese ondersoek. 'n Eenvoudige skermtoets wat onlangs beskrywe is[4] kan die dokter in staat stel om dié pasiënte wat geen ernstige siekte van die bloeiingsoort het nie, uit te skakel, maar pasiënte wat abnormale reaksies op hierdie toets toon verg moontlik 'n tromboplastien-vormingtoets. Met behulp van hierdie metode kan die diagnose met sekerheid bepaal word en kan pasiënte wat aan *Christmas*-siekte ly uitgeken word. Dit is ook baie nuttig as die hoeveelheid antihemofiliese globulien (AHG) in die sirkulerende bloed bereken kan word. Daar is 'n hele paar metodes hiervoor wat egter nie almal dieselfde resultate lewer nie. Die betreklik eenvoudige en toereikende metode wat deur Biggs[2] beskryf is, het reeds baie nuttig geblyk by die beplanning en beheer van die behandeling. Volgens hierdie metode word dit vasgestel dat ernstige bloeiers minder as 1 persent sirkulerende AHG besit; daarteenoor

EDITORIAL

HAEMOPHILIC HAEMORRHAGE AND ITS TREATMENT

Haemorrhage is always frightening, especially when it persists, but in most patients it can be controlled by relatively simple procedures. This is not the case in haemophilia, for these patients continue to bleed long after the bleeding points have been identified and ligated. Recent work, much of it from Britain,[1-3] has thrown new light on the problem of treatment.

Prophylaxis is of course the first essential, and much can be done to prevent trauma. Haemophiliacs bruise easily and should be handled as one handles overripe tomatoes! Haemophiliac boys should not be permitted to share all the physical activities of their contemporaries, however much we may wish to let them lead normal lives. Regular visits to the dentist may obviate troublesome dental extractions in later years and a very conservative attitude should be adopted towards surgery. All but the most essential operations must be avoided. The mortality rate from intra-abdominal surgical operations in haemophiliacs in almost any hospital in South Africa is today probably over 50%. This is much greater than the mortality rate for most acute abdominal emergencies treated without operation by modern conservative regimes; unrelieved acute intestinal obstruction is one of the notable exceptions to this generalization. Furthermore, most of the so-called acute abdominal emergencies in haemophiliacs are produced by haemorrhage into the gut or muscle wall; these too usually subside with non-operative treatment.

Correct diagnosis of the blood condition is essential and this involves a complete haematological work-up. A simple screening test that was recently described[4] may enable one to eliminate those patients who have no serious bleeding disorder of the haemophilic variety, but patients who give abnormal results with this test may need a thromboplastin-generation test. By this means the diagnosis can be confirmed with certainty and patients with Christmas disease recognized. It is also of great help if the level of circulating antihaemophilic globulin (AHG) can be estimated. There are a number of methods of doing this which do not all give exactly the same results. A relatively simple and adequate method,

is 30 persent die hoeveelheid wat teenwoordig moet wees vir behoorlike bloedstelping. Gevalle wat minder ernstig aangetas is (die term ‚ligte gevalle' word doelbewus vermy) kan selfs tot 30 persent sirkulerende AHG besit. Hoe meer AHG die pasiënt het, hoe geredeliker kan die bloeier se gebrek aangevul word en hoe minder moeilikheid kan met bloeding verwag word.

Om die hoeveelheid sirkulerende AHG te vermeerder kan ons vars plasma, òf gekonsentreerde preparate van AHG afkomstig van mense of diere gebruik. Pasiënte met *Christmas*-siekte kan doeltreffend met plasma wat nie meer so vars is nie behandel word, of selfs met serum; dit is die rede waarom dit so belangrik is om by die diagnose *Christmas*-siekte van hemofilie te onderskei. Vars normale plasma kan maklik in 'n hospitaal bekom word, maar omdat die AHG so labiel is, is dit noodsaaklik dat dit, wanneer dit by hemofilie gebruik word, onmiddellik voor gebruik gekollekteer word. Menige klein operasie soos die trek van 'n tand of insny van 'n abses kan gedoen word ná die toedien van (ten minste) 'n liter plasma. Die plasma moet vinnig toegedien word (binne 'n uur) en die operasie moet so beplan word dat dit begin wanneer die oortapping eindig. By 'n minder ernstig aangetaste bloeier sal hierdie hoeveelheid plasma die hoeveelheid AHG tot op 30 persent te staan bring, maar by ernstiger gevalle sal dit nie so hoog styg nie, hoewel dit hoog genoeg mag loop om 'n klein operasie moontlik te maak. Dit sal by hierdie ernstiger gevalle nie toereikend wees vir groot operasies, veral buik- en borskasoperasies, nie. Die uitwerking van die oortapping sal nie lank hou nie; binne 11 uur verdwyn 50 persent reeds, en binne 24 uur gaan die meeste van die aktiwiteit verlore. Gedurende die na-operatiewe periode sal die hoeveelheid AHG gewoonlik onder 30 persent bly as die pasiënt net een oortapping daagliks ontvang, sodat oortapping meer dikwels nodig is. Die behandeling moet voortgesit word totdat die herstel goed gevorder het—dit mag 'n tydperk van 3 tot 21 dae beslaan. 'n Groot aantal bloedskenkers sal dus benodig word, en hoewel die rooi bloedselle nie weggegooi hoef te word nie maar vir ander pasiënte gebruik kan word, beteken dit tog dat daar veel van die skenkerdiens (en/of die dokter se tyd) geverg word. Die meeste pasiënte wat as bloeiers uitgeken word besit minder as 1 persent sirkulerende AHG en hierdie prosedure sal hulle dus nie red as daar enigiets ernstiger as 'n baie klein operasie gedoen moet word nie. Macfarlane en sy medewerkers in Oxford[1] was die baanbrekers in die gebruik van gekonsentreerde AHG afkomstig uit varke of beeste. Met behulp van hierdie preparate kan betreklik enorme dosisse AHG toegedien word—genoeg om 'n hoeveelheid van meer as 30 persent oor 'n aansienlike tydperk in stand te hou. Op hierdie wyse was hulle in staat om groot operasies uit te voer en 'n hele paar lewes is reeds gered. Ongelukkig is hierdie stowwe ook antigenies en hulle kan ook plaatjiearmoede veroorsaak. Die reaksies op hierdie stowwe begin ontwikkel 10—14 dae nadat die pasiënt hierdie behandeling ontvang het, en dan mag die antigeniese stof nie verder gebruik word nie. Dit is gelukkig dat pasiënte wat sensitief is vir een van hierdie stowwe nog die ander mag ontvang. As 'n pasiënt eers 'n gevoeligheid vir die stof ontwikkel het, bly hy heelwaarskynlik sy hele lewe lank gevoelig, en dus mag die stowwe nie gebruik word behalwe by die uiterste noodgevalle nie. Die pasiënte het bloot een, of

described by Biggs,[2] has proved very useful in planning and controlling therapy. By this technique severe haemophiliacs have been shown to have less than 1% circulating AHG, as against 30%, which is the level required for adequate haemostasis. Less severely affected cases (the term 'mild' is deliberately avoided) may have anything up to 30% circulating AHG. The more AHG he has, the easier is the haemophiliac's deficiency correctable and the less trouble with haemorrhage is to be anticipated.

In order to raise the level of circulating AHG we can use either fresh plasma or concentrated preparations of AHG derived from human or animal sources. Patients with Christmas disease can usefully be treated with plasma which is not so fresh or even with serum; hence the importance of this differentiation in the diagnosis. Fresh normal plasma can be made readily available in most hospitals, but because the AHG is very labile it is essential when it is to be used for a haemophiliac that it be collected immediately before use. Many minor operations like the extraction of teeth or the incision of abscesses can be conducted after the infusion of (at least) a litre of plasma. This must be rapidly transfused (within an hour) and the operation timed to start as the transfusion finishes. This amount of plasma will raise the level of AHG in a less severely affected haemophiliac to 30% but in the more severely affected patient the level will not reach so high. It may, however, be high enough to allow minor surgery to be performed; it will not suffice for major, especially intra-abdominal and intrathoracic, surgery. The effect of transfusion will not last for very long; in 11 hours about 50% will have disappeared, and the bulk of activity will be lost within 24 hours. During the post-operative period, if the patient only receives one transfusion a day, the level of AHG will be below 30% for most of the time, so that more frequent transfusions will be required. Treatment must be continued until healing is well advanced and this may be for a period of 3–21 days. A large number of donors will thus be required, and while the red cells need not be discarded but can be used for other patients, the drain on the donor service (and on the doctor's time) will still be considerable. The majority of patients classed as haemophiliacs have less than 1% circulating AHG and this procedure will not serve if they require anything more than a minor operation. Macfarlane and his co-workers at Oxford[1] have pioneered the use of concentrated AHG derived from pig or beef sources. By the use of these substances relatively enormous doses of AHG can be given, sufficient to maintain levels of over 30% for a considerable time. In this way they have been able to carry out major surgery and a number of lives have already been saved. Unfortunately these materials are antigenic and may also cause thrombocytopenia. Reactions to the material start to develop after the patients have received treatment for 10–14 days and preclude the further use of the offending substance. Fortunately, patients sensitive to one of these substances can

miskien twee, ekstra kanse ontvang; in elk geval is die stof nie maklik bekombaar nie. Stof van menslike oorsprong is reeds voorberei[5] maar dit is nog nie heeltemal bevredigend nie en die voorrade is moontlik nog meer beperk.

Dit is altyd wenslik om die uitwerking van oortapping te bereken deur die AHG-hoogte 15 minute na die voltooiing van die oortapping te meet. Indien die hoogte nie genoeg gestyg het nie, het die preparaat wat gebruik is minder AHG dan beweer word (en die meeste van die sogenaamde antihemofiliese preparate wat vandag bemark word kom in hierdie klas voor), of anders reageer die pasiënt nie normaal nie. 'n Stollingsteenstof in die bloedsomloop, wat nogal dikwels by hemofilie voorkom, kan ook so 'n uitwerking hê. Sommige pasiënte reageer glad nie, sonder enige voor die hand liggende rede.[2] In elk geval sal 'n kennis van die reaksie op oortapping die chirurg in staat stel om daaropvolgende behandeling te beplan en om verdere dosering te bereken. Plaaslike behandeling is belangrik en moet nooit afgeskeep word nie. Die bloeipunte moet waar moontlik afgebind word, selfs al beteken dit dat dit toegewerk moet word. Wonde moet versigtig verbind word en die verband moet styf op sy plek gehou word sodat dit nie kan skuif en die rou oppervlakte beskadig nie. Rekverbande (*one-way-stretch*), met 'n kussinkie van sponsrubber om die druk meer eweredig te versprei, is baie nuttig. By ernstige gevalle is spesiale spalke, pleisters of beddens soms nodig om die beseerde liggaamsdeel onbeweeglik te hou. Besmetting is gevaarlik aangesien sekondêre bloeding nog meer moeilikheid as die primêre soort kan veroorsaak. Indien die verband om hierdie rede afgehaal moet word, moet AHG-inhoud dadelik weer vermeerder word *voor* daar met die operatiewe prosedures begin word.[1] Indien tande getrek moet word, word afsonderlik voorbereide, deursigtige akriliese spalkies voor die operasie gemaak en hulle oefen 'n sagte druk op die bloedingspunte uit.[3]

As die bloeding nie deur plaaslike maatreëls stopgesit kan word nie, is dit nutteloos en selfs skadelik om die bloeding te probeer beheer deur plaaslik meer druk uit te oefen. As die bloeding voortgaan, moet die bloed toegelaat word om te ontsnap. Oormatige druk op 'n bloeiende tandkas kan miskien net die bloed na die nek of middelvleis afkeer en die pasiënt kan versmoor. Bloed in die spiere van 'n ledemaat kan ischiemiese nekrose veroorsaak. As daar enige tekens hiervan voorkom, moet die steke verwyder word en die druk verlig word. Daar is maar net een manier om hierdie probleem op te los en dit is om die sirkulerende AHG tot op bloedstelpende hoogtes te bring.

Ten slotte: 'n Bloeier se lewe kan daarvan afhang of daar are beskikbaar is vir oortapping. As die diagnose eenmaal deeglik beklink is, is dit nie nodig om elke keer as hy in die hospitaal opgeneem word 'n volledige diagnostiese ondersoek van die stelpingstatus te doen nie. Dik naalde vir aarpunksie kan gevaarlik wees, terwyl ‚cut downs' en daaropvolgende afbind van are 'n hoogs benodigde aar prysgee. Dit is gewoonlik moontlik, met genoeg versigtigheid en geduld, om met 'n dun naald in 'n aar te dring. Selfs as aartrombose na veelvuldige gebruik voorkom, sal die are dikwels 'n ander kanaal vorm, mits hulle nie afgebind was nie, en sal hulle weer beskikbaar wees vir gebruik by een van daardie desperate noodgevalle wat nog maar steeds die lot van die bloeier is.

1. Macfarlane, R. G., Mallam, P. C., Witts, L. J., Bidwell, E.,

still receive the other. Once sensitized, patients probably remain so for life so that these materials should not be used for anything but desparate emergencies. The patients have merely been granted one or perhaps two additional chances; in any case supplies are not readily available. Material derived from human sources has been prepared[5] but is as yet not entirely satisfactory and supplies are likely to be even more limited. It is always advisable to assess the effects of transfusion by estimating the AHG level 15 minutes after the transfusion has been completed. If the level has not risen adequately then either the preparation used has even less AHG than it is reputed to have (most so-called antihaemophilic preparations which are commercially available at the present time fall into this category) or else the patient is responding in an abnormal way. A circulating anticoagulant, not infrequent in haemophilia, may produce this effect. Some patients fail to respond without obvious cause.[2] In any case a knowledge of the response to transfusion will enable the surgeon to plan subsequent treatment and to gauge further dosage. Local treatment is important and should never be neglected. Bleeding points must be secured when possible even if this means putting in a stitch. Wounds must be dressed with care and the dressing kept firmly in place without any movement which might damage raw surfaces. One-way-stretch bandages and sponge rubber padding to distribute pressure evenly are helpful. In serious cases special splints, plasters or beds may be required to immobilize the injured part. Sepsis is dangerous since secondary haemorrhage can be even more troublesome than the primary variety. If dressings are to be disturbed on this account then the AHG level must once again be raised *before* the operative procedures are commenced.[1] When teeth are to be extracted, individually prepared transparent acrylic splints are made before the operation and these exert gentle pressure on the bleeding points.[3]

If local measures fail to stop the bleeding it is useless and harmful to attempt to control the haemorrhage by increasing local pressure. Constant watch must be kept for signs of local tension. If bleeding is continuing then the blood must be allowed to escape. Excessive pressure on a bleeding tooth socket for instance may merely succeed in diverting the blood into the neck and mediastinum and the patient may die of suffocation. Blood in the muscles of the limb may cause ischaemic necrosis. If there are signs of this then the stitches must be removed and the tension relieved. There is only one way to handle this problem and that is to raise the circulating AHG to haemostatic levels.

One final point: The life of a haemophiliac may depend on the availability of veins for transfusion. Once the diagnosis has been adequately established there is little point in performing a full diagnostic work-up of the coagulation status every time the patient is admitted to hospital. Thick needles for venipuncture may be dangerous while 'cut downs' with subsequent tying of veins sacrifice a much-needed vein. With sufficient care and patience it is usually possible to enter a vein with a thin needle. Even if veins should thrombose after repeated use, provided they have not been tied they will often recanalize and become once again available for use in one of those desperate emergencies which are still the lot of the haemophiliac.

1. Macfarlane, R. G., Mallam, P. C., Witts, L. J., Bidwell, E.,

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A REVIEW OF HYDATID DISEASE OF THE BRAIN

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Of all the parasites infesting the brain, the larval stage of one or other of the cestodes or tapeworms is by far the commonest. By and large, parasitic infestation of the brain is of rare occurrence and does not lend itself to ready diagnosis and, at best, can only be strongly suspected in sheep-rearing countries, when the doctor is confronted with a patient under middle age, with raised intracranial pressure and angiographic changes suggestive of a large cyst out of all proportion to the amount of disability produced. It is clear that the condition should be suspected on clinical grounds, and further investigated by angiography rather van ventriculography, in order to eliminate the danger of puncturing the cyst with resultant dissemination of daughter cysts and the almost inevitable recurrence. This is only true when dealing with hydatid disease caused by the larval stage of *Echinococcus granulosus*, and this paper will deal with this type in some detail; the other types will merely be mentioned, as they are rarer, present a different clinical picture and offer a different diagnostic problem.

1. The larval stage of *Echinococcus granulosus*:

The adult tape worm is commonly found in the duodenum of the dog and other carnivora, and when full-grown is 3–6 mm. long, consisting of four segments—a scolex, which carries four suckers and a double row of hooklets; the immature proglottid; the mature proglottid, followed by the terminal gravid segment, which carries from 500 to 800 ova in various stages of development.

The ovum, 45 μ in diameter, and brownish in colour, has a chitinous envelope which is resistant to heat and cold. When swallowed by the intermediate host, it hatches into an active hexacanth embryo, which makes its way into the portal vein and is carried throughout the body. The majority of the embryos are filtered out in the liver, the commonest site for hydatid disease; the next commonest is the lungs and the spinal column and the brain follow in lesser frequencies.

Within a very short time a cyst develops with fluid on the inside of the germinal epithelium and a laminated membrane of hyaline material on the outside, which constitutes the true capsule of the bladder-like cyst. A false capsule forms around the developing cyst, which is a fibroblastic reaction by the host; this is seen in the brain as a flimsy neuroglial reaction. Not all of the germinal epithelium is fertile, but budding occurs at a thousand places, growing towards the cyst cavity as scolices, daughter cysts and grand-daughter cysts in various stages of development. They become characteristically detached from the parent cyst wall and occur as 'hydatid sand' or sediment in the parent cyst.

There is always a tendency for a hydatid cyst to become multi-vesicular, but multi-loculation or exogenous budding of brood capsules appears to be an effect of pressure exerted by the tissues of the host, particularly irregular pressure. This is well demonstrated by our series, where all the cysts except one was single when the site was in the brain, in contrast to the multiple cysts encountered in the spinal column.

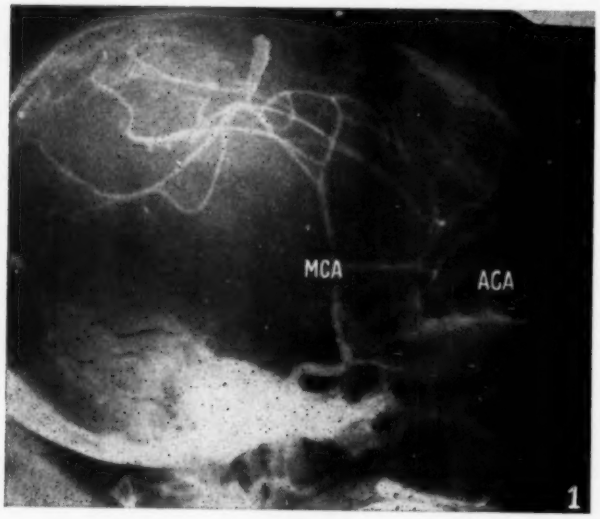
The cysts are slow-growing and may reach a large size before producing symptoms. If lodged in the spinal column they produce symptoms earlier and do not reach a size greater than 1 cm. in diameter before the patient seeks medical advice.

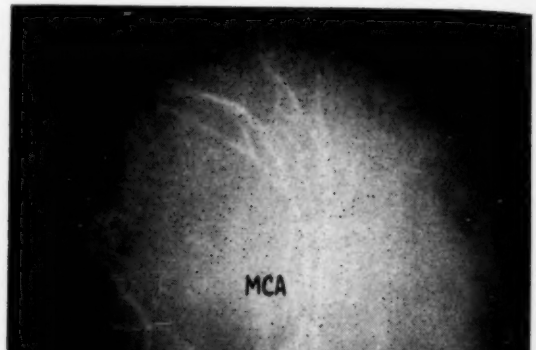
The nerve tissues are not infiltrated but are pressed aside by the developing cyst. It shows some predeliction for the cerebrum, and is decidedly rare in the cerebellum. The symptoms are characteristically intermittent due to intermittent oedema, but the reason of this phenomenon is still unknown.

2. *Cysticercus cellulosae*, the larval stage of *Taenia solium*, a cestode or tape worm commonly found in man. Humans can be infected by swallowing the eggs passed in human faeces, or by regurgitation of the intestinal contents into the stomach as a result of gastric disturbance, which is equivalent to swallowing thousands of eggs, or by ingesting pig's flesh in the uncooked form.

The liberated oncosphere penetrates the intestinal wall and gains access into the lymphatic or blood stream to be disseminated into the muscles, subcutaneous tissue, eye and brain. The resulting bladder worm, *Cysticercus cellulosa*, measuring 5 × 8 mm., shows a great tendency to calcify and be diagnosed with great facility by taking plain X-rays of the brain and muscles of a suspected case. When lodged in the brain they tend to produce epilepsy.

3. *Coernurus cerebralis*, the larval form of the tape worm, *Multiceps multiceps*, found in the brain of man, sheep, goats, cattle and antelopes. The cysts are smaller, up to 2 cm. in diameter, and are usually multiple. They are found in the





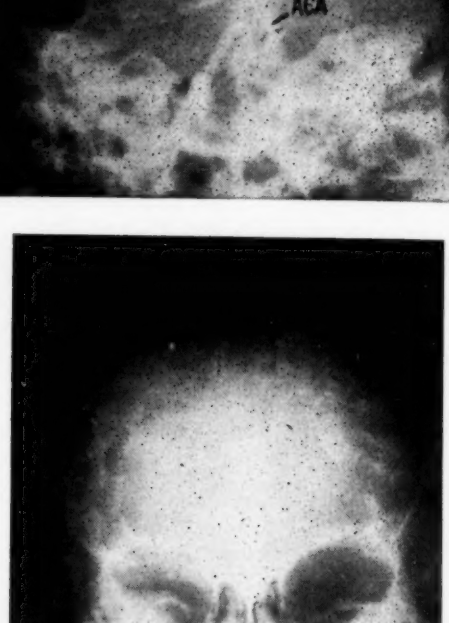


Fig. 1. The lateral projection shows elevation of the middle cerebral vessels (M.C.A.) actively stretched over an avascular space-occupying mass in the right fronto-temporal region.
Fig. 2. A.P. Projection shows marked displacement of the middle cerebral artery (M.C.A.).
Fig. 3. Lateral projection showing numerous calcified cysticerci.
Fig. 4. A.P. projection showing a calcified extra-dural hydatid cyst.
Fig. 5. Lateral projection showing a ventriculogram and a large hydatid cyst in the third ventricle.
ACA=Anterior cerebral artery.

cerebrospinal fluid pathways causing a hydrocephalus, with increased protein and cells in the cerebrospinal fluid. They vary in shape and are often found in clusters. Through the semi-transparent cyst wall, the cloudy contents can be seen, which are calcified bodies and not scolices. Clusters of scolices can be made out on the inner wall, and remain characteristically attached to the wall of the cyst.

MATERIAL

The present study is based on a series of 20 cases of hydatids in the central nervous system, of which 14 had the cysts in the brain and 6 in the spinal column.

HYDATID DISEASE OF THE BRAIN

1. J.G. (E.M.) Age 18: Three months before admission he complained of weakness of the right limbs, followed by pain in the neck, nausea and vomiting two months later, and double vision ten days before admission. On examination, papilloedema and right hemiparesis. Blood picture normal. X-rays of skull: signs of increased intracranial pressure. Ventriculogram abnormal. Site: Left fronto-parietal. A single cyst, 5 cm. in diameter was removed. Complete recovery with occasional fits. No recurrence.

2. H. de K. (E.F.) Age 13: 7 months before admission she developed a right hemiparesis, followed by headaches and double vision 4 months later. Jacksonian seizures set in 4 days before admission. On examination, bilateral papilloedema and right hemiparesis. Blood picture normal. X-rays of skull: normal. Electro-encephalogram: abnormal. Ventriculogram showed left parietal mass. A single cyst, 6 cm. in diameter, was removed. She made a partial recovery, with an occasional seizure. Three years later she had only a slight residual hemiparesis and the last seizure had occurred 8 months previously.

She presented a year later with increasing weakness of the right limbs and dysphasia. Angiography revealed a large cyst in the left parietal region. At operation a large cyst was removed, which proved to be a porencephalic cyst and not a recurrence of the hydatid disease.

3. P.K. (E.M.) Age 23: 5 months before admission he experienced headache and difficulty to concentrate. Two months later he noticed a right temporal field defect and tremors of the right hand. Two weeks before admission he experienced spells of diplopia and a mild dysphasia became noticeable, superimposed on his previous tendency to stutter. On examination, bilateral papilloedema; right lower temporal quadrantic field defect; slight dysphasia and weakness of the left side of the face, of a central type. X-rays of skull: normal. Electro-encephalogram: abnormal. Blood picture normal. Angiography revealed a cyst in the left temporo-parietal region. At operation a large, left temporo-parietal cyst, 7 cm. in diameter, was removed. Complete recovery followed. A year later a moderate-sized hydatid cyst was removed from the left trapezius muscle.

4. D. v. Z. (E.M.) Age 12: 3 months before admission he experienced right-sided Jacksonian fits, a month later, right hemiparesis and 2 months later, headache and nausea. On examination he had a right hemiparesis and papilloedema. Skull X-ray showed springing of sutures. Normal leucocyte count. Electro-encephalogram abnormal and angiogram suggestive of a cyst. Two large hydatid cysts were removed from the left parietal region. Complete recovery.

5. A.J. (C.F.) Age 5: Progressive weakness of lower limbs and right upper limb, and difficulty with micturition for six months. On examination the patient was found to have bilateral papilloedema and a right hemiparesis, including the face. Skull X-rays showed springing of the sutures. Blood count within normal limits. Ventriculogram demonstrated a large fronto-parietal mass on the left side, extending to the midline; and marked dilatation of the lateral ventricles. At operation a large, single hydatid cyst was removed from the left fronto-parietal region. The child died three days later.

6. J.A. (C.M.) Age 17: Weakness of the right leg for 2 years, followed by weakness of the right arm 18 months later. Headaches and deterioration of vision for 3 weeks. On examination, bilateral papilloedema with secondary optic atrophy and old haemorrhages. Right spastic hemiparesis. X-rays of the skull abnormal, showing prolonged pressure effect. Blood count within normal limits. Angiogram showed a large left fronto-parietal avascular space-occupying mass. At operation a large hydatid cyst was removed. The hydatid skin test was negative and the flocculation test positive when these were done post-operatively. When discharged, 3 weeks later, he had some residual weakness of the right foot.

7. D.K. (C.F.) Age 19: A few days before admission, the patient became aware of weakness of the right limbs, headache and diplopia. On examination, bilateral papilloedema with exudates, and paresis of the right limbs, including the face. Reflexes brisk on the right side and a right extensor plantar response. X-ray of the skull showed a small area of calcification in the left cerebral hemisphere. Angiography confirmed an avascular mass in the left parietal region. At operation a single, large hydatid cyst was removed from the left parietal region. She made a complete recovery.

8. P.K. (E.M.) Age 5: The patient developed weakness of the right side 6 months before admission, followed by headaches and fits. On examination, he presented with a right hemiplegia, including the face; bilateral papilloedema. Ventriculography demonstrated a mass in the left lateral ventricle. At operation a large hydatid cyst was removed from the left lateral ventricle. Complete recovery resulted.

9. (E.M.) Age 46: Headaches and fits for one year. On examination no abnormal neurological signs could be demonstrated. X-ray of the skull showed a calcified mass in the left frontal region. A large calcified hydatid cyst was removed from the left frontal region. Complete recovery.

10. M.C. (E.F.) Age 9: A week before admission, the child developed peri-orbital swelling of the left eye. followed by headache, vomiting and unsteadiness on the feet a few days later. On examination, bilateral papilloedema; partial third cranial nerve palsy on the left; and a right facial paresis. Blood picture normal. X-rays of skull, abnormal. Ventriculogram demonstrated a space-occupying lesion in the left fronto-temporal region. At operation a large extradural cyst was removed, followed by complete recovery.

11. D.J. (C.F.) Age 13: One year previously she had a generalized epileptic seizure, followed by a left hemiparesis 6 months later. Headache and vomiting shortly before admission. On examination, bilateral papilloedema and a left hemiplegia, including the face. Electro-encephalogram abnormal. Blood count within normal limits. Angiography demonstrated an avascular mass in the right temporo-parietal region. At operation a large, single hydatid cyst, 8 cm. in diameter, was removed. She made a full recovery.

12. P.N. (C.M.) Age 18: 15 months before admission, the patient felt dizzy on standing or walking. One month later he experienced weakness of the left limbs. On examination, a left spastic hemiplegia, including the face, was found. Blood picture normal. Lumbar puncture—normal pressure and normal constituents. Ventriculography demonstrated a large, right temporo-parietal tumour which, at operation, was found to be a large, single hydatid cyst. Complete recovery took place.

13. C.H. (C.F.) Age 50: Patient complained of weakness of the left limbs for four weeks before admission. On examination she had bilateral papilloedema with haemorrhages; and a left hemiplegia. Ventriculography demonstrated a right parietal mass. She died 6 hours after ventriculography. At autopsy, a hydatid cyst of the right parietal region was found.

14. C.W. (C.F.) Age 34: 4 months before admission the patient experienced pain in the frontal region of her head, accompanied by vomiting; 3 months later her vision deteriorated. On examination there was bilateral papilloedema and moderate visual field constriction. Paresis of the right rectus oculi muscle. Electro-encephalogram—abnormal. Ventriculography demonstrated a large filling defect of the posterior part of the third ventricle. A right frontal craniotomy was performed and the third ventricle explored through the right lateral ventricle, but no tumour was encountered. 1 c.c. of Myodil was instilled into the third ventricle, which outlined the whole of the third ventricle. The patient died

and at autopsy, a small cyst, 3 cm. in diameter, was found, which proved to be a hydatid cyst on histology.

HYDATID DISEASE OF THE SPINAL COLUMN

1. G.N. (C.M.) Age 42: 3 years before admission the patient experienced backache. Two and a half years later he experienced pain in both legs, aggravated by coughing; followed by weakness of both legs and difficulty in initiating micturition; and a band of numbness of the left groin. On examination, weakness of both legs; depression of vital sensation in the sacral dermatomes and in the T 12 to L 3 dermatomes on the left side; and patchy depression of sensation on the right side. The abdominal and cremasteric reflexes were absent on the left side—knee and ankle jerks absent on both sides. X-rays of the spine showed erosion of the left pedicle of Lumbar 1 vertebra. Lumbar puncture showed a complete block, with 1,600 mgm.% protein, globulin +++ and 2 lymphocytes. Myelography showed a complete block at L 1. At operation a large number of small hydatid cysts were removed from the extradural space at L 1 and 2. On discharge, a month later, there was minimal residual weakness of the legs and only slight depression of sacral sensation.

2. J.J. (C.M.) Age 12: 4 months before admission he developed a sudden pain in the back, followed by paraplegia a few days later. He had experienced difficulty with micturition during the latter 2 months. On examination, the patient presented with a spastic paraparesis, with only slight movement in the feet: diminution of vital sensation below L 1; sense of position and passive movements defective in knees, ankles and toes. Reflexes very brisk and bilateral ankle and knee clonus; bilateral extensor plantar responses. Lumbar puncture was performed and only a few drops of cerebrospinal fluid obtained. X-rays of the spine showed a paravertebral shadow and some destruction of the body of T 11. A small, single hydatid cyst was removed at T 11. He made an incomplete recovery, only in so far as sensation and joint sensation were concerned.

3. S.B. (E.F.) Age 18: This patient experienced numbness of the left leg 7 months before admission, followed by numbness of the right leg a month later. Weakness of the legs set in 3 months later, and she was unable to walk for the 2 weeks immediately before admission. On examination there was a spastic paresis, with only minimal movement in the right foot. Vital sensation was lost below the level of L 1 and joint sensation absent in all the joints below the knees. Reflexes were increased. Lumbar puncture revealed cerebrospinal fluid that clotted on standing, and Queckenstedt's test was positive. Myelography demonstrated a complete block at T 10. At operation, 3 small hydatid cysts were removed at T 10. She made a complete recovery.

4. M.T. (E.F.) Age 70: One month before admission she experienced girdle pains, aggravated by movements. Two weeks later, she woke up one morning to find her legs completely paralysed. She was numb below the umbilicus and had difficulty in passing urine. (Coughed up a hydatid cyst two years previously.) On examination, there was a flaccid paralysis of both legs; vital sensation depressed below T 9, and sense of position and passive movements lost in the legs. Abdominal and deep reflexes of the legs abolished. Blood picture normal. Casoni test negative. Myelography demonstrated a complete block at T 10. Several small hydatid cysts were removed from the extradural space at T 10. Incomplete recovery resulted.

5. D.B. (E.F.) Age 10: Clumsiness of the legs was noticed 6 weeks before admission, and patient unable to walk for 5 days before admission. On examination, a spastic paraparesis; depressed sensation to pin-prick below T 8; position and motion sense not affected; knee and ankle jerks brisk; abdominal reflexes absent and bilateral extensor plantar responses. X-rays of the spine showed erosion of the pedicle of T 6 on the left side. Lumbar puncture revealed a low pressure and an impeded rise and fall on jugular compression. Protein 450 mgm.% and 4 lymphocytes. Myelography demonstrated a complete block at T 5/6, and several hydatid cysts were removed from the extradural space. Recovery was incomplete.

Improvement continued for 2 years, when she developed weakness of the legs and difficulty with micturition. On examination a spastic paraparesis was present and loss of deep sensation in both legs. Myelography demonstrated a partial block at T 4/5 and a complete block at T 12. A laminectomy at this level revealed adhesions due to arachnoiditis. No improvement followed and she was again explored at T 4/5 and 20 small and one large hydatid cysts were removed. Recovery was rapid and virtually complete.

6. M.L. (E.F.) Age 26: The patient developed weakness and numbness of both legs 3 months before admission. On examination, spastic paraparesis of both legs and vital sensation depressed below T 7. Myelography demonstrated a complete block at T 4. Cerebrospinal fluid showed protein value of 127 mg.%. At operation several hydatid cysts were removed from the extradural space at the level of T 4. Complete recovery resulted.

DISCUSSION

In our series, 6 of the 14 cerebral cases were children. There were 7 females and 7 males. The age does not affect the manner in which the disease manifests itself. It is commoner in the young adult—only 3 cases were older than 23 years of age. All of them had resided on farms for the major part of their lives.

Ten of the 14 cerebral hydatids presented with hemiplegia. 6 had focal or generalized epilepsy at one or other stage of the disease. 10 experienced headache due to raised intracranial pressure. 12 of the 14 cases had papilloedema. All but one case had single cysts—average 7–13 cms. in diameter. All the cysts were supratentorial, 1 in the extradural space, 8 in the left hemisphere, 1 in the left ventricle, 3 in the right hemisphere and 1 in the third ventricle. All the cases were

TABLE I. DATA IN 14 CASES OF HYDATID OF BRAIN

Case	*Age in Years*	*Duration of Symptoms before Operation (months)*	*Headache*	*Fits*	*Hemiplegia*	*Papilloedema*	*Site (Hemisphere)*	*Result*
1	18	3	−	+	+	+	L	Cured
2	13	7	+	+	+	+	L	Improved
3	23	5	+	−	−	+	L	Cured
4	12	3	+	−	+	+	L	Cured
5	5	6	−	−	+	+	L	Died
6	17	24	+	−	+	+	L	Improved
7	19	1 week	+	−	+	+	L	Cured
8	5	6	+	+	+	+	L	Cured
9	46	12	+	+	−	+	L	Cured
10	9	1 week	+	−	−	+	L	Cured
11	13	12	+	+	+	+	R	Cured
12	18	15	−	−	+	−	R	Cured
13	50	1	−	−	+	+	R	Died
14	34	4	+	−	−	+	IIIrd ventricle	Died

operated on and histologically confirmed. 3 cases died—1 after investigation by ventriculogram.

None of the cases had demonstrable hydatid disease elsewhere in the body. 1 developed hydatid cysts in the trapezius one year after the original operation—1 had coughed up a hydatid cyst 2 years before. No case had a recurrence of the disease in the brain.

The condition can be strongly suspected on clinical grounds when a young adult or child presents with headaches, hemiparesis, fits and papilloedema of gradual onset, and further investigations should be restricted to angiography rather than ventriculography for fear of puncturing a posteriorly situated cyst. Roma-Arana-Iniquez *et al.* drew attention to the characteristically fine, bilateral tremor, not accentuated by closing the eyes, and disappearing shortly after operation. The aetiology is obscure, but it may be a toxic element or the effect of generalised pressure on the basal nuclei.

We have long ago discarded the hope that eosinophilia, skin reactions or complement fixation tests are of any help. Some workers have tried the antigen obtained from human hydatids, with better results. Plain X-rays of the skull are not helpful in differentiating it from other space-occupying lesions. They may show signs of raised intracranial pressure, such as erosion of the clinoids, springing of the sutures, silver-beaten appearance of the skull and displacement of the calcified pineal. When calcified, it cannot be differentiated from calcifying tumours, arteriovenous anomalies, or tuberculomata.

Ventriculography should be avoided when there is associated hemiplegia, or when hydatid disease is suspected on clinical grounds. This is in sharp contrast to *Cysticercus cellulosae* and *Coenurus cerebralis*, which very commonly block the cerebrospinal fluid pathways, in which case ventriculography, supplemented by Myodil ventriculography is the chief means of investigation.

Angiography is the ideal method of investigation and, more often than not, the condition can be correctly diagnosed. There is usually gross displacement of the vessels, circumscribing a regular avascular area, typical of a cystic mass. The size of the 'tumour' is usually surprisingly big and not in keeping with the extent of physical disability produced.

Electro-encephalography is not very helpful and there is nothing pathognomonic in those performed on our cases. None of our cases demonstrated an area of electrical silence surrounded by delta waves—as described by Foster, Castells and Gastant. In our cases diffuse abnormality throughout the brain, suggestive of hydrocephalus, and delta wave activity in the region of the cyst, surrounded by an area of delta wave activity of high voltage, are more usual.

TREATMENT

The treatment of hydatid disease of the central nervous system, is the removal of cysts *in toto*, without rupturing them. Many methods have been described, but we have found the method described by San Julian *et al.* to be the easiest and most efficacious. It involves a liberal craniotomy, the location of the cyst by means of a brain cannula, used very gently to avoid puncturing the cyst wall, followed by an incision through the cortex in a radial fashion. The line of cleavage between brain and cyst is defined, and further isolation of the cyst is effected by a gentle jet of water through a catheter, the tip of which is inserted between cyst and brain, assisted by gravity by tilting the head, so that the cyst is lowermost.

The mortality rate is low, the morbidity rate low and, in most cases, the recovery is complete. In the spinal cases, all improved and 3 made complete recoveries.

SUMMARY

The pathology of hydatid disease has been discussed, with special reference to the differentiation of hydatid disease caused by the larval stage of *Taenia echinococcus* from *Taenia solium* and *Multiceps multiceps*.

The clinical diagnosis, or suspicion, is important in order that further investigations be restricted to angiography, rather than ventriculography. The left hemisphere is by far the commonest site. Treatment is by means of enucleation assisted by a jet of water, and gravity. The prognosis is good.

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NEW HORIZONS IN THE CHEMOTHERAPY OF MENTAL DISEASE*

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It is not to the novelty of the new tranquillizing drugs that I must pay tribute for the great pleasure I am afforded in speaking before you, but to their popularity. In the United States the consumption of these medicines has soared at a fantastic and alarming rate since they first were hesitantly placed on the market in 1954. It is claimed that in total sales, tranquillizing drugs are exceeded only by antibiotics and vitamins. It has indeed become Big Business in the best American tradition. Even in Great Britain, concern has been expressed over a similar situation. I can speak only for the United States when I express the opinion that the medical

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profession has relinquished a considerable measure of its authority in the face of public demand. The word tranquillizer has achieved an honoured place in the several advertising and entertainment media—radio, TV, the ladies' magazines and of course on Wall Street. American psychiatry, sundered by ideological conflict, has failed to adopt a definitive position in this matter. In consequence, the bulk of physicians had little authority to resist the demands of their patients for the 'magic pills' on the one hand; and on the other the blandishments of skilful salesmen from the pharmaceutical houses. In fact, in the case of one or two of these drugs, illicit drug-store sales without prescription became commonplace. The psychiatrist has traditionally been a clinician, unsophisticated in the field of investigation. Necessary requirements by drug houses for clinical trials of their drugs overtaxed the few psychiatrists willing to try them, with the inevitable sequel of hurried, uncontrolled reporting, and sometimes unreasonable claims. On at least one occasion introduction of a new drug with mass advertising has preceded any report on its value in the literature. It has truly been a deplorable state of affairs.

Objective appraisal of the tranquillizers is hard to extract out of what is literally a public debate. I will give you my opinion for what it is worth. It is at least the critical opinion of one who has been associated with the development of these agents for therapeutic purposes since 1953. Given judiciously and systematically, the more powerful tranquillizers such as chlorpromazine are more effective in the treatment of schizophrenia and states of excitement than any other treatment, chemical or otherwise. In neurotic patients and normal individuals suffering from an excess of tension, all the tranquillizers may afford symptomatic relief. To what extent this is significantly greater than that afforded by other treatments is not clear. It is abundantly clear, however, that there is often no more justification for their prescription in this latter group of patients than there is for placebos or a sea voyage. It is to be hoped that the fad will soon pass, and with it the erroneous concept that personal inadequacies in the face of daily problems are susceptible to chemical solution. The path will then be clearer for the consolidation and enhancement of the notable gains these drugs have already made in the treatment of the seriously mentally ill.

The use of drugs to treat nervous and mental afflictions is as old as the hills. Aldous Huxley has commented that stimulating and depressant herbs were known to primitive man long before he had learned to till the soil. Even one of the brightest stars in the ataractic galaxy, reserpine, was employed by Indian physicians many centuries ago. The modern chemotherapeutic era in neuropsychiatry was ushered in by the discovery in France in 1952 of the unusual sedative properties of chlorpromazine. Shortly thereafter, the chemically dissimilar but pharmacologically related, reserpine was isolated from the old Indian snakeroot plant. Both these compounds enjoyed immediate success in clinical psychiatry and both produced sufficiently interesting effects upon the central nervous system to excite the interest of the laboratory workers. In consequence, many other similar substances have been synthesized and some marketed. And in addition, some notable advances in our understanding of central nervous system function may be expected in the near future.

What is a tranquillizing drug? No satisfactory definition of the term has ever been given. For my part, bromide and phenobarbital are good tranquillizers. If one were to except these on the grounds that they impair cortical function as they sedate, one would still have to include morphine as a tranquillizer. On this basis too, meprobamate (Equanil), perhaps the most popular of them all in America would be omitted, since in large doses it does cause mental confusion. To side-step controversy, one may say that there are two classes of tranquillizers. The phenothiazine series, of which chlorpromazine is the parent, and the reserpine derivatives comprise the powerful tranquillizers. Meprobamate, phenaglycodol (Acalo) and hydroxyzine (Atarax) represent the milder tranquillizers. While adequate criteria for their use are still not determined, the first group is in greatest demand for the psychotic patient and the mild group for the ubiquitous tension and anxiety states.

There are too, other drugs not classed as tranquillizers which must be considered. Many new non-barbiturate hypnotics have been developed in recent years (methylprylon) in the hope that they would lack the addictive properties of the barbiturates. It is doubtful whether this hope has, or can be, realized. Any drug which relieves anxiety, does not have unpleasant side-effects, and which in cumulative doses tends to euphoria, will be addictive in some individuals. It is well worth noting that the powerful tranquillizers like chlorpromazine have not offered convincing evidence of habituation, possibly because of unpleasant side-effects and lack of euphorizing qualities. Clear cases of meprobamate addiction, however, are to be found in the literature, complete with reports of withdrawal syndromes almost identical with those following deprival of barbiturates.

Benactyzine (Suavitil, Parasan) is an anti-cholinergic substance investigated by Jacobsen, the discoverer of Antabuse. In some patients it produces a state of well-being and is free of noxious side-effects. However, in many it evokes feelings of depersonalization and interruption of thought processes which are intolerable. It remains to be seen whether it will survive its clinical debut.

A number of other miscellaneous chemicals which includes lysergic acid diethylamide (LSD), ipronazid and various serotonin antagonists are in process of exploration both in laboratory and ward. They will be mentioned again later.

Lastly upon the chemotherapeutic horizon are to be seen the central stimulants, personified of course by amphetamine. Despite a number of recent introductions, e.g. ritalin, meratran, and a great deal of painstaking research, there are no major advances to report in the past 15 years.

The phenothiazine series of compounds is worthy of further consideration. Chemically rather simple, they are constructed upon the triple 6-carbon ring phenothiazine molecule in which two of the carbon atoms are replaced by a single nitrogen and sulphur atom. Attached to the nitrogen atom is a one to four membered carbon side-chain terminating in a substituted amino group. Later phenothiazines have a nitrogen-containing ring structure in place of the simple amino group (piperazine or piperidine). In some members of the series a halogen atom is added to the phenothiazine nucleus.

Small changes in chemical constitution appear to bring about considerable differences in pharmacology. For

example, drugs with the amino side-chain like chlorpromazine or trifluorpromazine (Vesprin) evoke many peripheral autonomic effects such as hypotension, dryness of mouth, etc. When this is replaced by a piperazine ring, autonomic effects are inconspicuous but extrapyramidal signs become commonplace. It is not possible to go further into the details of these correlations in this paper.

The therapeutic and toxic effects of chlorpromazine are well established and little needs to be said here. The author has always believed that intensive dosage with rapid increments of the drug to the limit of tolerance (which may run above 3,000 mg. daily) is the most successful and economical way of treating the acute or chronic schizophrenic patient. For manic and delirious cases where inhibition of motor activity is the primary concern, lower doses usually suffice. Despite clinical trials with over a dozen phenothiazines, none has proved therapeutically a great deal better than chlorpromazine. However, as is well known, this agent is handicapped by a multitude of side-effects, idiosyncratic responses such as jaundice and dermatitis. In very high doses it may cause confusion or convulsions. Substitution of fluorine for chlorine, as in Vesprin, appears to reduce, but not eliminate autonomic effects and also increases potency weight for weight. Exclusion of any halogen moiety as in promazine (Sparine) greatly reduces therapeutic potency except in so far as sedation is concerned. For this reason promazine is a good intravenous sedative and is used quite extensively for this purpose in alcoholic patients. In larger doses, it has had, in the author's hands, a convulsive incidence approaching 25% and cannot be recommended for the treatment of schizophrenic patients. Passing over a number of others in this group because of excessive toxicity or therapeutic mediocrity, we arrive at the piperazine phenothiazines. These have in common, a high potency—therapeutic doses averaging one tenth of that of chlorpromazine, a slower onset of action, progressively increasing sedation (the reverse tends to be true for chlorpromazine) and a powerful action on the extrapyramidal system. Prochlorperazine (Compazine), trifluorperazine (SKF 5019) and perphenazine (Trilafon) are in this class. While essentially similar, the latter two drugs appear to be more successful therapeutically than compazine. Since the literature at present contains only one or two references, it may be of interest to consider Trilafon in more detail.

TRILAFON

Thirty-seven psychotic patients were treated by a standard intensive method using Trilafon. With the exception of one case of Huntingdon's chorea, they were all schizophrenic. 17 suffered with acute illness (less than 6 months duration) and 19 had been ill for periods ranging from 9 months to 15 years. Females outnumbered males by two to one. Dosage of Trilafon ranged from a minimum of 4 mg. daily (in a child) to 208 mg. daily. Average length of intensive treatment, i.e. before discharge from hospital or cessation of treatment, was just over one month. About one half of the patients continued to receive a maintenance dose in the out-patient clinic. Where necessary, the drug was given in equivalent dosage intramuscularly until the patient was able to take it orally. No other treatment was administered during the period of study. Clinical results were classified as follows:

Recovered	5
Substantially improved (able to leave hospital)	13
Improved symptomatically	13
Unimproved or worse	7

Most of the patients in the last two categories were as might be expected those with chronic illness.

The following side-effects were encountered:

	%	
Persistent drowsiness	55	21
Gastric distress	8	3
Hypotension	8	3
Lactation	3	1
Dermatitis	3	1
Weakness	8	3
Parkinsonian syndrome	50	19
Dystonia (torsion spasm)	23	9

Lactation is a highly sporadic and interesting sequel to phenothiazine therapy. We have noted it with several of the phenothiazines. The secretion when analyzed proves to be true milk. While this was not so with the trilafon patient, lactation induced by other drugs has sometimes been accompanied by menstrual irregularities, not, of course, associated with the pregnant state.

Extrapyramidal syndromes are a most impressive aspect of phenothiazine treatment. It will be noted that the incidence with Trilafon is 50%. This is also true of Compazine and SKF 5019. With these drugs parkinsonism appears with doses of 30 mg. daily and up varying of course greatly in different individuals. It is always reversible upon reducing dosage or discontinuing the drug. The disorder is characterized by rigidity, some tremor, salivation, masking of the face and gait difficulties. The onset of this condition is frequently preceded by several days of restlessness and feelings of tension. Some investigators have considered this to be anxiety and have offered a psychodynamic theory in explanation. The author, however, regards it as acathisia—the motor restlessness described by Wilson. In addition, to parkinsonism, Trilafon produces two other neuromuscular abnormalities. Dystonic symptoms or torsion spasm may precede or develop independently of parkinsonism. One 12 year old schizophrenic girl developed spasm of the left neck muscles and shoulder girdle after a single dose of 4 mg. It sometimes has an explosive onset and may be almost epileptic in appearance. More usually, it persists for several days with periods of exacerbations sometimes involving the whole of one side of the body, but generally restricted to the neck and shoulders. A further side-effect is also likely an extrapyramidal manifestation. Complaints of dysphagia are made without parkinsonism or dystonia. On examination there is to be found localized rigidity of the tongue and pharyngeal muscles without actual incoordination of the swallowing mechanism.

While the aetiology of these fascinating effects is not clear, they are reproducible in monkeys, and in laboratories we have been attempting to find neuro-histological and bio-electric correlations of these disorders of function.

Benzotropine methanesulfonate (Cogentin) is highly effective in relieving these extrapyramidal symptoms when they become bothersome to the patients. Given parenterally, the effect is almost immediate. Cogentin also has a stimulant effect upon those who are lethargic from Trilafon—though not on normal individuals. Possibly there is a yet undiscovered neurophysiological relationship between sedation and

parkinsonism as induced by these drugs. It should be stressed that parkinsonism is rarely seen with doses of less than 30 mg. daily and is always reversible. Whether or not it is related to, or is necessary for a good therapeutic result is an open question. In the opinion of this author, it is not, and we do not deliberately attempt to produce the condition.

We have also used Trilafon to treat tension in small numbers of non-psychotic patients in doses of up to 24 mg. daily. With the exception of lethargy, there were no complaints of side-effects. Reduction of tension was variable, ranging from almost total relief to none at all.

Children appear to be especially sensitive to Trilafon, as Table I below indicates. This is somewhat unexpected in view of the fact that chlorpromazine is usually better tolerated by children than by adults.

TABLE I. EFFECTS OF TRILAFON ON EXTRAPYRAMIDAL SYSTEM

Sex	*Age*	*Diagnosis*	*Dose at onset*	*Day of Treatment*	*Disorder*
F	12	Schizophrenia	4 mg. (1st dose)	1	Dystonia Dyspagia
M	4	Schizophrenia	4 mg. daily	5	Parkinsonism
M	13	Neurodermatitis	4 mg. bid	3	Dystonia
F	12	Behaviour Disturbance	4 mg. tid	64	—
F	9	Behaviour Disturbance	4 mg. tid	6 months	—
M	16	Schizophrenia	5 mg. qid (IM)	4 days	Dystonia Parkinsonism

In summary, Trilafon is a highly potent drug which exerts beneficial effects upon acute and chronic schizophrenic patients which are as good as or better than with other phenothiazines. Side-effects of consequence comprise several variants of extrapyramidal dysfunction when the dosage is increased over 30 mg. daily (though they may appear with less). (See Table I).

It is necessary to exercise caution in giving it to children since the appearance of dystonia, while not dangerous, is certainly very alarming to the parents.

We are currently investigating two other phenothiazine drugs in the hope of finding one which has the high potency of Trilafon but without the extrapyramidal action. So far, however, almost all the really effective phenothiazines have caused this condition to some extent.

Reserpine and other alkaloids from Rauwolfia also produce parkinsonism as well as a multiplicity of effects, very much like chlorpromazine. We use reserpine seldom for the following reasons. It has a slow and somewhat unpredictable time of onset of effect. The ratio between parkinsonism and therapeutic level is small. It has a tendency to produce depressive reactions which may reach psychotic proportions. This property is shared to a much lesser degree with chlorpromazine. Depressive reactions have been notably frequent with the use of reserpine in treating hypertension. Despite the dissimilarity of chemical structure, the actions of reserpine and chlorpromazine are remarkably alike.

THE 'CENTRAL-RELAXANT' DRUGS

The term central-relaxant has been coined to describe a number of other drugs introduced in the past few years. They share muscle-relaxant properties which can be demonstrated experimentally, and sedative properties with little or no action upon the autonomic nervous system. In general, side-effects are few and they give none of the striking neurophysiological changes of the phenothiazines. In toxic doses, they produce confusion, coma, and ataxia, although the margin of safety is high. Meprobamate (Miltown or Equanil) is a derivative of the older drug mephenesin which itself had muscle-relaxant properties but was not found too effective clinically. Meprobamate has enjoyed enormous popularity in the United States and has been used indiscriminately by the public. In therapeutic doses of 400 mg. three or four times a day, it has a mild sedative action and a quieting effect upon the tense or agitated. Muscle spasm, especially when of psychogenic origin, is diminished. In somewhat larger doses, meprobamate may lead to mild euphoria, and in excessive dosage produces mild symptoms of intoxication very reminiscent of barbiturate or alcohol intoxication.

Meprobamate is even more limited in usefulness in the treatment of psychotic patients than are barbiturates. It is not a useful hypnotic in the presence of severe insomnia or agitation.

Despite its popularity, there is no clearly incontrovertible evidence to indicate that meprobamate is superior to barbiturates or bromide for the treatment of psychoneurotic and tension symptoms. Controlled studies are difficult to achieve and the therapeutic influence of other variables may well exceed that of the drug itself. In several attempts at controlled and double-blind studies to evaluate meprobamate, the author's group found it less effective than a placebo on one occasion, and more effective than phenobarbital on another.

The site and mode of action upon the nervous system is controversial. A specific change in thalamic electrical activity has been described without associated alteration in cortical leads. However, typical barbiturate-like fast EEG activity has been reported by others.

It seems that addiction to meprobamate does occur. Lemere in Seattle has reported several cases who developed severe withdrawal symptoms after discontinuance. The author has also seen two cases, both women, who were taking 4,800 mg. daily or more. Within 36 hours after withdrawal, they became irritable, confused and had grand mal seizures for several days.

As long as man reacts to stress with unresolved tensions, so long will he seek relief by one means or another. Meprobamate and to a lesser extent chlorpromazine and reserpine drugs are in fashion just now. The author fails to believe that these agents are specifics for anxiety. What advantage they enjoy over their predecessors lies chiefly in their lessened toxicity.

Phenaglycodol (Acalo) is a chemical cousin of meprobamate which has been recently introduced. Somewhat

more potent milligram for milligram it is essentially similar in action and side-effects. Clinical reports are too few to make an assessment at present.

Hydroxyzine (Atarax) is an antihistaminic drug which has sedative and muscle-relaxant properties with some mild autonomic effects. It is used in the same way as meprobamate.

Interest in the central stimulant drugs has increased of late because of their antagonism to the sedative and depressing properties of most of the tranquillizers. A number of stimulant-tranquillizer combinations are on the market. Their value is doubtful because there is so much individual variation in responsiveness to these drugs. In one patient, the stimulation is dominant, in another sedation is paramount. Meretran and Phenidylate are two recent non-amphetamine introductions. The author considers them less satisfactory than dextroamphetamine or desoxy-ephedrine, though they are perhaps better antagonists of reserpine-induced depression. A really good cerebral stimulant is still wanting.

HALLUCINOGENS

The subject matter of the remainder of this paper is more theoretical though no less controversial. The story of the Swiss chemist Hoffman's accidental discovery of lysergic acid diethylamide is well known by now. The substance, derived from ergot, belongs to the group of hallucinogenic agents. Very probably a majority of the drugs in the pharmacopoeia would cause hallucinations if the dose were sufficiently large. Atrophine, cortisone and mapharside are common examples. The term hallucinogen is best reserved for chemicals which in relatively small doses cause a temporary and reversible psychotic state as their main effect. LSD is unique in that doses of 20 millionths of a gram will do this. It is possible to secure measurable effects with as little as 4 millionths of a gram. The psychosis is undoubtedly a true exogenous toxic type of reaction with hallucinations, delusions, impairment of judgment, memory and orientation. However, it frequently bears a close resemblance to an acute schizophrenic reaction. On this account LSD is being used in experimental psychiatry as an experimental tool in schizophrenia research. Under the influence of the LSD psychosis patients may recall forgotten events, and release anxiety which has caused some to employ it adjunctively to psychotherapy. Good results are claimed. In passing, it may be said that schizophrenic patients, particularly chronic ones, are resistant to LSD and show minimal effects with even massive quantities.

LSD is also a powerful antagonist to serotonin. Serotonin or 5-hydroxy-tryptamine is thought to be an important neurohumor mediating inhibitory nerve impulses in the central system. Theories have been advanced that too much, or too little serotonin in the brain is responsible for menta! disturbance, Irponiazid (marsalid) which will be mentioned again inhibits the enzyme mono-amine oxidase which normally destroys serotonin. In consequence, serotonin accumulates in the brain. Since iproniazid itself may produce a psychosis in large doses, the theory gains support. Reserpine administration on the other hand, appears to interfere with the power of the brain to bind serotonin, which is excreted in large quantities as its breakdown product, hydroxy-indoleacetic acid. Free circulating serotonin then, is responsible for the typical reserpine effects. It is supposed while these observations are highly attractive there are too many gaps and contradictions to justify great optimism. BromLSD for example, which is an even more potent inhibitor of serotonin than LSD does not produce psychoses. Further, chlorpromazine which is the most effective blocking agent of the LSD psychosis does not release serotonin.

Acting on the plausible assumption that an excess of serotonin has at least some connection with abnormalities of brain function, work is in progress to develop anti-serotonins—antimetabolites, of which a number of already known. Preliminary clinical trials have been disappointing.

Another substance which is coming into prominence as a hallucinogen is bufotenine found in toads, cohoba snuff and probably in some poisonous mushrooms. It is very closely related to serotonin, being dimethyl tryptamine. These, and other observations form the foundation of the 'Indole hypothesis' which postulates that a defect in the metabolism of indole-containing substances in the body leads to production of brain poisons in the body which in turn underlie mental illness.

This hypothesis has been linked with anoher hypothesis—the 'Adrenaline theory', since by a sort of tchemical leger-demain breakdown products of adrenaline can be viewed as indole derivatives. Catabolites of adrenaline have already been reported as causing artificial psychoses—notably adrenochrome and adrenoxin, which incidentally are formed in the course of time in vials of commercial adrenaline—giving so-called pink adrenaline. Further support is lent this hypothesis by the fact that mescaline, another well-known hallucinogen obtained from the North American cactus (Peyote) is chemically similar to adrenaline.

Unfortunately, these theories, attractive though they are, fail to recognize clearly that an artificial psychosis is in fact a delirium of special type—a disorder reflecting almost any disturbance of brain metabolism as, for example, anoxia or high fever. Unfounded though they may prove to be, it is highly encouraging to witness the almost daily strides being made in elucidating the process of brain metabolism. Consequential to this will be the synthesis of valuable clinical weapons. Iproniazid, one of a number of inhibitors of monoamine oxidase is such a one. Supposing there to be a deficiency of serotonin in the brain tissues in states of depression, the addition of iproniazid ought to help by reducing serotonin breakdown. Early clinical trials are said to be promising.

It would indeed be possible to continue longer in this vein but my time is up. Psychopharmacology or, if you prefer, neuropharmacology is growing up. Whether it is still in the neonatal period or whether it is nearing maturity is not yet clear. As a result of the research of the past five years, all the new tranquillizing drugs may fall by the wayside, but at least we have a road along which to travel.

A COMPARISON OF URINARY OESTROGEN LEVELS IN NORMAL MALE SOUTH AFRICAN BANTU AND EUROPEAN SUBJECTS

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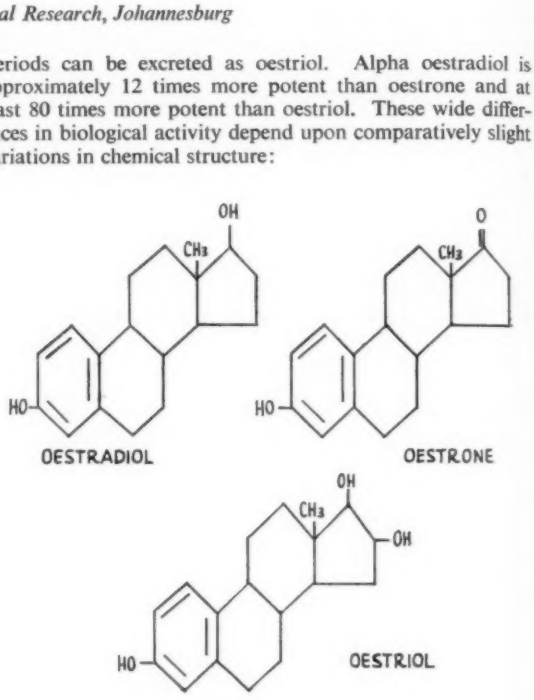
In the South African Bantu, the frequency of biochemical dysfunction of the liver is well known, being present in over two-thirds of adults examined, the great majority of whom show no clinical symptoms.[1-2] Further, hepatic cirrhosis is present in about 10% of adults examined at necropsy, while hepatic fibrosis and primary carcinoma of the liver are much more prevalent in the Bantu than in the European population.[3-8]

The liver exerts an important influence on hormonal metabolism in maintaining the delicate balance between oestrogens and androgens. In chronic liver disease, disturbance of sex hormone balance is frequently encountered. Thus, menstrual disturbances frequently occur in the African female and gynaecomastia, testicular atrophy, loss of pectoral and axillary hair, loss of libido, and impotence, are commoner in African than in European males.[9] Gillman and Gillman[10] have alluded to the correlation between gynaecomastia and testicular atrophy on the one hand and liver damage, on the other. These authors, however, state that they were unable to correlate the presence or absence of gynaecomastia with the extent or severity of the pathologic changes in the liver. Davies[11] suggested that the different incidence of a number of pathological states in the African from that found in European subjects might be due in the first instance to the high incidence of liver disease caused by malnutrition, and then that, as a result of the hepatic dysfunction, the Africans are subjected to wholesale oestrinization from an early age.

The liver plays a dominant role in normal individuals in the intermediate metabolism of oestrogens. This view is supported by observations on laboratory animals, human subjects and by *in vitro* experiments.[12-17]

Experiments on normal male subjects indicate that after intramuscular injections of large doses of oestrogens so much of the hormone is lost in the process of intermediate metabolism that only relatively small quantities are recovered from the urine. This major loss of oestrogenic activity is variously described as being due to destruction, inactivation or conversion of the hormone by the liver.[16] Thus, injected oestrogens, in the presence of a normally functioning liver, lose much of their activity but, in the presence of liver disease, high concentrations of oestrogen are recovered. The greater the degree of liver damage, the greater is the failure to inactivate or convert endogenous, as well as exogenous, oestrogens.[16]

The oestrogenic steroids are oestradiol, oestrone and oestriol. The oestradiol fraction may be regarded as the true oestrogenic hormone and the oestrone and oestriol fractions as breakdown products. Oestrone is an intermediary product in the transformation of oestradiol to oestriol. Schiller and Pincus[18-19] have shown that oestradiol and oestrone are interconvertible, and that both these steriods can be excreted as oestriol. Alpha oestradiol is approximately 12 times more potent than oestrone and at least 80 times more potent than oestriol. These wide differences in biological activity depend upon comparatively slight variations in chemical structure:



Until quite recently, reliable methods for the determination of urinary oestrogens were mainly confined to biological assays. In 1955 J. B. Brown[20] described a technique for the chemical estimation of urinary oestrogens. Marrian[20] in discussing this method, referred to it as being workable and convenient and accurate enough to determineas little as 5 μg. each of oestradiol, oestrone and oestriol in a 24-hour specimen of urine.

In view of the high incidence of liver disease in the South African Bantu and the important role played by the liver in steroid metabolism, we decided to investigate urinary oestrogen levels in normal Bantu male subjects and to compare our findings with those found in a similar group of normal European male subjects.

Material and Method

We obtained 24-hour specimens of urine from 21 European male subjects, who were members of the staff of this Institute and in excellent health, and from 21 Bantu male subjects. Of the latter, 15 were employed at this Institute and were in excellent health and 6 were patients suffering from minor surgical injuries but assessed clinically as normal and healthy. The age ranges and mean ages for the European

groups were 20—48 years (mean 30·5) and for the Bantu group 20—45 years (mean 31) years respectively.

The technique we used for estimating total oestrogen, oestradiol, oestrone and oestriol was that described by Brown.[20]

RESULTS

Tables I and II show the amounts of total oestrogen, and the absolute and relative amounts of the 3 fractions oestradiol, oestrone and oestriol, which we found in 24-hour specimens of urine from normal Bantu and European male subjects.

TABLE I. ANALYSIS OF THE OESTROGEN CONTENT OF 24-HOUR SPECIMENS OF URINE IN NORMAL BANTU MALE SUBJECTS

Total Oestrogen (μg.)	*Oestradiol* (μg.)	*Oestradiol* %	*Oestrone* (μg.)	*Oestrone* %	*Oestriol* (μg.)	*Oestrio* %
13·3	3·9	29·3	5·5	41·4	3·9	29·3
9·1	0·0	0·0	5·5	60·4	3·6	39·6
12·4	3·2	25·8	3·7	29·8	5·5	44·4
21·0	6·4	30·5	9·7	46·2	4·9	23·3
8·3	3·1	37·3	3·0	36·1	2·2	26·6
12·3	2·5	20·3	7·9	64·2	1·9	15·5
10·6	1·8	17·0	2·4	22·6	6·4	60·4
8·8	1·4	15·9	3·4	38·6	4·0	45·5
11·6	4·6	40·0	6·2	53·4	0·8	6·6
6·6	0·4	6·0	3·0	45·5	3·2	48·5
10·9	3·4	31·2	5·5	50·5	2·0	18·3
11·2	1·3	11·6	5·5	49·1	4·4	39·3
18·2	4·7	25·8	11·3	62·0	2·2	12·2
18·9	4·0	21·2	10·4	55·0	4·5	23·8
5·0	1·1	22·0	2·3	46·0	1·6	32·0
10·7	1·8	16·8	3·4	31·8	5·5	51·4
8·5	0·0	0·0	5·4	63·5	3·1	36·5
10·9	1·7	15·6	6·4	58·7	2·8	25·7
17·3	5·3	30·6	7·3	42·2	4·7	27·2
5·2	0·9	17·3	2·0	38·5	2·3	44·2
9·2	1·2	13·0	5·0	54·4	3·0	32·6
MEAN VALUES 21 SUBJECTS						
11·5	2·5	21·8	5·5	47·8	3·5	30·4

TABLE II. ANALYSIS OF THE OESTROGEN CONTENT OF 24-HOUR SPECIMENS OF URINE IN NORMAL EUROPEAN MALE SUBJECTS

Total Oestrogen (μg.)	*Oestradiol* (μg.)	*Oestradiol* %	*Oestrone* (μg.)	*Oestrone* %	*Oestriol* (μg.)	*Oestrio* %
4·4	1·1	25·0	2·7	61·3	0·6	13·7
13·1	2·2	16·8	3·8	29·0	7·1	54·2
6·1	2·9	47·5	2·0	32·7	1·2	19·7
10·9	0·7	6·4	9·8	89·9	0·4	3·7
7·2	0·8	11·1	4·4	61·1	2·0	27·8
7·6	0·9	11·8	3·4	44·7	3·3	43·5
4·7	0·0	0·0	3·0	63·8	1·7	36·2
5·7	0·0	0·0	3·6	63·2	2·1	36·8
4·6	0·7	15·2	2·5	54·3	1·4	30·5
13·7	0·9	6·6	2·9	21·2	9·9	72·2
4·6	1·1	23·9	1·7	36·9	1·8	39·2
7·3	1·8	24·6	3·7	50·7	1·8	24·7
10·2	1·2	11·8	7·4	72·5	1·6	15·7
9·7	0·6	6·2	6·3	64·9	2·8	28·9
3·8	0·2	5·3	2·9	76·3	0·7	18·4
8·7	2·0	23·0	4·7	54·0	2·0	23·0
15·4	3·1	20·1	9·0	58·4	3·3	21·5
6·5	0·4	6·2	3·6	55·4	2·5	38·4
9·9	1·9	19·2	6·7	67·6	1·3	13·2
9·2	1·0	10·9	4·1	44·6	4·1	44·5
8·3	0·0	0·0	4·1	49·4	4·2	50·6
MEAN VALUES 21 SUBJECTS						
8·0	1·1	13·9	4·3	53·7	2·6	32·4

The mean total urinary oestrogen value in the non-European was 11·5 μg. as compared with 8·0 μg. in the European.

The mean oestradiol value was 2·5 μg. in the non-European as compared with a mean value of 1·1 μg. in the European; whilst the percentages of oestradiol to total oestrogen were 21·8% and 13·9% respectively.

The mean oestrone value was 5·5 μg. with a percentage of 47·8 in the non-European as against 4·3 μg. and 53·7% in the European.

The mean oestriol value was 3·5 μg. and 30·4% in the non-European and 2·6 μg. and 32·4% in the European.

These results when subjected to statistical analysis show the following:

1. A very highly significant increase in the total oestrogen level per 24-hour specimen of urine in the non-European when compared with the European ($p = < 0{\cdot}005$).

2. A very highly significant increase in the absolute oestradiol level ($p = < 0{\cdot}005$) and a statistically significant increased percentage of oestradiol in the non-European ($0{\cdot}01 < p < 0{\cdot}025$).

3. No significant differences either in the absolute or relative amounts in the oestrone and oestriol fractions in the two racial groups.

DISCUSSION

Our results show, that even in the apparently 'healthy' South African male Bantu a significantly different oestrogenic pattern exists from that in the European counterpart. Thus, the Bantu shows a significant increase in total urinary oestrogen levels, as well as in the very active and potent oestradiol fraction. Our findings, when taken in conjunction with the available evidence of increased oestrogen levels in patients suffering from liver disease, further substantiates the known high incidence of liver impairment or dysfunction in the so-called 'normal' Bantu.

We have merely investigated urinary oestrogen levels, but available evidence exists that there is a multiglandular endocrine disbalance in liver disease, and one would probably find evidence in the normal Bantu of adrenal overactivity resulting in secondary pituitary depression leading to lowered urinary gonadotrophin levels.

Lloyd and Williams[21] suggest that the liver participates in steroid metabolism by aiding the interconversion of oestradiol and oestrone to oestriol, by the formation of inactive oxidative products from oestrogen, and in the conjugation of oestrogens for inactivation and excretion. They postulate that in liver disease there is a diminution in the release of follicle-stimulating hormone, a suppression of spermatogenesis and follicle maturation, and oestrogenic stimulation of target organs. Owing to the decrease in the inactive oxidative products there is a decreased release of the pituitary luteinizing hormone and adrenotrophin leading to menstrual disturbances, loss of axillary hair and diminished urinary 17-ketosteroid excretion.

The 'disease pattern' of the Bantu differs markedly from that of the European. Among the former, for instance, there is a high incidence of certain deficiency diseases, a high incidence of liver disease, especially primary carcinoma, and a low incidence of atherosclerosis, diabetes, gall-stones, peptic ulcer and certain forms of cancer.[22] Is it not possible that the altered pattern of disease in the Bantu is due to the marked hormonal and endocrine disturbances found in this racial group?

Davies[11] suggests that the functional capacity of the liver is impaired, owing to malnutrition at an early stage in

infancy. Further dietetic privations, especially if accompanied by acute and chronic infections, lead later in life to further hepatic damage. Thus, from an early age, owing to this liver damage, the African may be subject to over-oestrogenization. If this is the case, then general changes should occur in the physique and the disease pattern of the African should be profoundly altered. Evidence of feminization, gynaecomastia and alterations in the general body configuration should be evident. The endocrine glands would be affected and the incidence of certain endocrine disorders should be altered. This, in effect, is what Davies observed in Uganda.

So far as primary carcinoma of the liver is concerned, the known carcinogenic properties of oestrogens should lead in the African to a high incidence of carcinoma of the liver and, since oestrogenization occurs from an early age, then the age incidence of this type of cancer should be lower than the usual 'cancer age'. This in fact is what happens in the African.

A striking feature of the disease pattern in the Bantu is the low incidence of coronary atherosclerosis and low serum-cholesterol levels. Cannot this low incidence also be correlated with the high oestrogen levels in the Bantu? Eilert[23] has shown that increased oestrogen levels depress serum-cholesterol; and Boyle[24] has reported reduction in all serum lipids, including cholesterol, during long-term administration of oestrogens. Thus, alterations in the balance between male and female sex hormones arising from liver dysfunction may well be involved in the observed differences between cholesterol levels in African and European subjects and in the low incidence of atherosclerosis in the former.

The high incidence of liver disease and dysfunction in the South African Bantu is considered by many to be largely the result of malnutrition. Incidentally, loss of libido, gynaecomastia and testicular atrophy were also noted in the severe malnutrition of prisoners of war.[25] The different pattern of disease in the Bantu could thus be intimately connected with malnutrition and kwashiorkor in the African infant, and later in life repeated episodes of undernutrition, especially if accompanied by infection, lead to permanent liver damage. The frequency of certain diseases and the rarity of others could thus be due indirectly to nutritional changes in infancy which lead to hormonal imbalance in later life.

SUMMARY

1. Urinary oestrogen levels were determined in 21 normal male European and 21 normal male Bantu subjects.

2. Highly significant increases in the total oestrogen level and in the oestradiol fraction were found in the Bantu group.

3. An attempt is made to correlate the 'disease pattern in the Bantu' with liver dysfunction resulting in endocrine imbalance.

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LOCAL SENSITIZATION OF THE SKIN TO PARAFFIN GAUZE DRESSING

(CURATIO CARBASI PARAFFINI B.P.C.)

THEODORE JAMES

Pinelands, Cape of Good Hope

This small contribution is submitted to support the suggestion put forward by Ridley[1] that the inclusion of Peruvian balsam in the official paraffin gauze dressing is hardly justifiable. The paraffin gauze dressing under discussion goes by several proprietary names, such as Tulle Gras, Nonad Tulle, Jelonet, and Optrex Tulle. It can easily be prepared by the method described by McIndoe.[2] The fact that this official dressing contains 1·25% of balsam of Peru suggests that a pharmaceutical property is necessary for the preparation. The alleged virtues of the balsam were highly priced in the beginning of its long history. Today its value is much less but it is still widely used in the western world and most frequently as a topical dressing or application for superficial conditions such as wounds and ulcers, skin affections like scabies, eczema, alopecia, pruritus, and when indicated for the stimulation of epithelial growth. For long it has been used as an inhalant

for the treatment of upper respiratory tract disorders. In Martindale's Pharmacopoeia[3] there is a brief admonition, without explanation, 'to test for albumen in the urine before and during treatment'; the reason for this warning remains unknown to me.

CASE REPORT

In May of this year a young woman was deeply bitten over the front of the leg by a bull-terrier dog. The injured area of skin was cleansed with antiseptic and prophylactic antitetanus serum was injected. Two days later a precautionary injection of procaine penicillin was given because of possible damage to the tibial periosteum. Débridement was not carried out because of the strong tendency for dog-bites to suppurate, but a dressing of Nonad Tulle was applied. The patient was ambulant 1 week later but the paraffin gauze dressing to the injured leg was continued for another week. Inspection at this time revealed that the skin under the Nonad Tulle was slightly swollen, erythematous and covered with a fine vesiculation. This skin change was so exactly limited by the gauze dressing that the impression that the Nonad Tulle had provoked a reaction was inescapable.

It was uncertain to what ingredient of the paraffin gauze dressing the skin had become sensitized. Opportunely, Ridley's memorandum[1] came to my notice. In this he proved that the agent in the Nonad Tulle most likely to be responsible for the reaction of the skin was the balsam of Peru. He reported a similar reaction to Tulle Gras in 2 patients suffering from a hypostatic eczema of the legs which was markedly aggravated by the balsam. Patch tests proved strongly positive. Ridley says that when such an untoward reaction happens, however rarely, it is reasonable to doubt whether the continued incorporation of the balsam in the dressing can be justified, the beneficial effect being so slight. In the instance reported here the sensitization occurred in skin which had been normal excepting the points of trauma. In my case a patch test was distinctly positive, the control being *paraffinum molle album*.

The meagre reports on this drawback to the use of Peruvian balsam disclose that Andrews[4] recorded a contact dermatitis following its use as a perfume in a toilet preparation and Engelhardt in 1880, cited by Alexander[5], refers to its sensitizing property. Alexander himself regards it as a strong contactant capable of sensitizing 10% of patients should it be applied freely. Mention is also made by Schwartz, Tulipan, and Peck[6] quoted by Ridley, of the balsam as a skin irritant. This kind of paraffin gauze dressing is so very widely used in in-patient and out-patient casualty work that the frequency of the sensitization reactions, which delay cutaneous healing, is surely not adequately reflected in published memoranda. The purpose of this paper is to try to turn Ridley's suggestion into a plea that the balsam of Peru be excluded from the official preparation *curatio carbasi paraffini* and, if it be thought necessary, that some other proven non-sensitizing substance be found to substitute for it.

SUMMARY

Evidence is presented to support a recommendation that the balsam of Peru included in the official paraffin gauze dressing in the B. P. C. does not appear to justify its inclusion because of its potential harmful sensitizing effect.

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DOCTOR TOPPER TAKES A TURN

What time is it? What day is it? How long have I been here? Shall I ask the figure in white? No. It is too much effort. Anyway, it does not matter.

I sink back into the limbo from which I wakened—the mist produced by hypnotic drugs. Gradually I become aware of my surroundings. I do not see the anxious faces round my bedside. I realize that for the first time in days I am alone. The crushing precordial pain has left me; there now remains only a feeling of discomfort. The sense of impending dissolution of a few days ago has given place to a new hope. I know that I am going to recover. That recovery will be slow and painstaking. I shall be out of action for six weeks or more. That will be the longest spell of inactivity I have ever known. A strange feeling of resignation possesses me. In a sense I have become re-orientated. The things I considered important have become less so, now.

After 25 years in practice I am now able, for the first time, to take stock of myself. My mind goes back to the years of childhood—life at home where everything contributed to smooth my path. Circumstances there were ideal for physical and mental development. Life at University was successful and happy. I was an average, hard-working student who found time for social activities and sport. Success crowned all my undertakings. After graduating I won recognition in my work at hospital, where I proved, by concentrated hard work, to be a popular and promising doctor.

After a fairly all-round experience I started out in general practice. From the outset I adopted a principle of all-out service. I took the uphill course; no stone was left unturned in the interest of the patient. My life became geared to a high pitch. I enjoyed the hard work, but I found that gradually all other interests became subservient to my singleness of purpose—the pursuit of success. Social life and sport were reduced to a minimum; the time I spent with my family and the enjoyment of home life became less and less. My clinical problems occupied my waking hours at night. Material return followed. A graph of my monthly takings became the measure of success. My attitude towards people changed; individuals were assessed in terms of potential fees; the approach to a given clinical problem now was, 'How much return would it pay?' I did not like this change, but accepted it without resistance.

My attitude towards my colleagues became dominated by the competitive spirit. They were all good men, and I wanted very much to preserve their goodwill and friendship. My overriding ambition often made me say things and do things which were contrary to their interests. I was discreet enough, however, not to expose myself to charges involving the ethical code. I was circumspect in observing the letter of the law.

By now I had gained the confidence of the community. Patients left their welfare unreservedly in my hands—in any decision their attitude was, 'Do as you think best, Doctor'. As I look back now I must confess I abused that confidence. I gave treatment that was not really necessary. I launched forth on undertakings that could have been performed better by those with specialized training. Anyway, 'I got away with it', and that seemed to be all that mattered at the time. The patient was none the wiser, and his confidence in me was unimpaired. This being the case, why should I consider the man who devoted years of study to a particular field? In my arrogance I did not see why I should consider anybody but myself. I developed the faculty to a very high degree of explaining away my mistakes to myself and to others. I reached the stage of self-assurance where mistakes could hardly come into my orbit at all. The world was at my feet.

Another of my achievements was the presidency of the local Branch of the Association. There the general discussions were on a level with those of the Chamber of Commerce; the theme was the profit motive. Material benefits accrued in proportion to my expenditure of energy. In the course of years I had accumulated money and all the things that go to make life comfortable and pleasant. But I did not have time to enjoy much of these, really. For me, the fun seemed to be in the acquisition of this world's goods more than in their use.

Religion played no part in my life. That was something which offered comfort and solace to the poor, the ignorant and the simple-minded. I had no need for the things of the spirit. In my self-sufficiency there was no need to turn to anybody for help. The Bible to me was no more than a fairy tale. My 'scientific' mind refused to accept the truth of the scriptural writings. In any case, I had no time for these things.

Then I came face to face with a most remarkable Personality. When I saw Him in person I realized why His influence had continued down the ages since the days when He walked on earth. I was rather afraid of what He would say to me. I expected Him to criticize me, to find fault and condemn me. He made no reference to my irregularities and transgressions. He need not have done so. In His presence I saw them in all their magnitude for the first time. He put His finger on the spot for me. The fault lay, He said, in my dedicating my life to the worship of false gods—the gods of material things. Then, with infinite understanding, He showed me His way of life.

PASSING EVENTS : IN DIE VERBYGAAN

Mr. Hymie Katz, Ch.M., who was in specialist surgical practice at 408 Dumbarton House, Church Street, Cape Town, has now moved to 302 Medical Centre, Heerengracht, Cape Town. His telephone numbers remain unchanged, viz.: Consulting rooms 3-0090, residence 6-8468.

* * *

Dr. Sidney Stein, of 602 Medical Centre, Heerengracht, Cape Town, has recently returned from overseas by air, accompanied by Mrs. Stein. Dr. Stein attended the recent International Congress of Dermatology, and visited dermatological centres in Zurich, London, and in the United States of America.

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Council for Scientific and Industrial Research; South African Bureau of Standards. A Lecture by Dr. E. J. Marais, Director of the National Physical Research Laboratory, on 'The Use of Radio-Isotopes in Industry and Industrial Research', will be held at 8 p.m. on Tuesday, 19 November 1957 at Electricity House, Strand Street, Cape Town. All are welcome. Admittance free.

SELECT LIST OF RECENT ACCESSIONS TO THE MEDICAL LIBRARY, UNIVERSITY OF CAPE TOWN

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NEW PREPARATIONS AND APPLIANCES : NUWE PREPARATE EN TOESTELLE

Donasil

Westdene Products (Pty.) Ltd. announce the introduction of Donasil for the treatment of premenstrual tension, and supply the following information.

Donasil therapy is based on symptomatic treatment and efficiently controls the syndrome of premenstrual tension. Donasil contains no hormones and therefore does not interfere with the physiological evolution of the cycle or the endocrine balance. It is a safe, non-toxic approach to treatment rapidly effective. Treatment is started 5-7 days before menstruation, or when the first signs of tension are noticed. It is discontinued as soon as the menstrual flow sets in.

Donasil is a combination of a diuretic and an antihistamine, having the following formula:

Amino-methyl-propanol-bromotheophyllinate, 50 mg.
Pyrilamine maleate, 30 mg.

Manufacturers: Dr. A. Wander S.A., Berne, Switzerland.

* * *

'Pen-Vee' Oral Benzathine Penicillin V Tablets

Wyeth Laboratories (Pty.) Limited announce the introduction of a new acid-stable oral benzathine penicillin V tablet under the trade name Pen-Vee and supply the following information. Each tablet contains 200,000 units (125 mg.) of N,N'dibenzylethelenediamine-di-(phenoxymethyl penicillin).

Benzathine penicillin V is relatively insoluble in gastric juice and is therefore 'self protected' against acid degradation. On the other hand it is readily soluble in the alkaline media of the intestinal tract, providing rapid though bland concentrations. Proof of this is that blood levels following the administration of Pen-Vee tablets are comparable with those obtained with the acid penicillin V. The blood levels are much higher than those obtained with equivalent oral dose of potassium or procaine penicillin G.

The following are the main advantages of Pen-Vee Tablets:

1. Rapid onset of action, with higher blood levels.
2. Reliable absorption—*minimal* destruction in the stomach—*maximal* absorption in the duodenum.
3. Sustained blood levels on 6-8 hourly dosage.
4. Well tolerated and virtually non-toxic.
5. Taken without regard to meals.
6. Scored tablets to facilitate lesser dosage if desired.
7. Stable for 24 months without refrigeration.

Pen-Vee Tablets provide an oral penicillin preparation with injection performance.

Packed in bottles of 36 scored tablets.

* * *

Rice Protein Improved with Lysine

E. I. du Pont de Nemours and Company (Inc.), Wilmington 98, Delaware, USA, introduce Du Pont L-lysine hydrochloride ('Daroyl'), containing 95% L-lysine HCl and 5% D-lysine HCl, and supply the following statement:

Significant improvement in the nutritive value of rice protein has been gained by adding L-lysine at the rate of 1 lb. per 1,000 lb. of white rice, according to Dr. Hans R. Rosenberg, nutrition expert of the Du Pont Company's Stine Laboratory.

Speaking at the International Nutrition Conference in Paris on 27 July 1957, Dr. Rosenberg described a series of 5 experiments in which weanling rats were fed with lysine-supplemented white rice. Male rats receiving the lysine-fortified rice grew 41% faster, and females 44% faster, than another group on the same diet, but with unfortified rice.

This indicates that supplementation of rice with lysine may be of great benefit to the many millions of human beings for whom rice is the staple diet.

L-lysine is one of 8 amino acids which are considered essential to human growth and health. All 8 must be present in food protein in correct proportions if the body is to receive full benefit from the diet. The proteins in meat, milk, eggs, fish, and cheese contain a proper balance of the essential amino acids, but many foods, particularly those based on cereal grains, do not. In the case of wheat this deficiency can be corrected by the addition of small quantities of lysine. Similar supplementation of rice is indicated in the light of Dr. Rosenberg's experiments.

Since lysine cannot be manufactured by the human body, the recent development by the Du Pont Company of a relatively inexpensive method of producing it from agricultural materials may make a significant contribution to human nutrition.

Reports of current research indicate that the protein needs of human beings generally parallel those of the test animals selected. Further experiments are directed at determining requirements of human beings at various stages of life—pregnancy, infancy, adolescence, maturity, and old age, as well as during illness and convalescence.

REVIEWS OF BOOKS : BOEKRESENSIES

OPERATIVE SURGERY. VOLUME 2

Operative Surgery. Volume 2. *Abdomen.* (Completion.) Under the General Editorship of Charles Rob, M.C., M.Chir., F.R.C.S. and Rodney Smith, M.S., F.R.C.S. Pp. viii + 407 + (4) (Index). 530 Illustrations. (This work will consist of 8 Volumes at £5 10s. 0d. for each volume and an Index at £2 0s. 0d.) London: Butterworth & Co. (Publishers) Ltd. South African Office: Butterworth & Co. (Africa) Ltd., P.O. Box 792, Durban. 1956.

Contents: (Sections I and II of Part III: Abdomen, are contained in Volume One.) *Part III. Abdomen.* (Completion.) *Section III: Hernia.* Congenital Diaphragmatic Hernia. Hiatus Hernia—Trans-Thoracic Approach. Hiatus Hernia—Abdominal Approach. Epigastric Hernia. Umbilical Hernia. Ventral and Scar Hernias. Inguinal Hernia. Femoral Hernia. Retro-Peritoneal Hernia. Rare Hernias. Internal Hernias: Hernia of the Bladder. *Section IV: Appendix, Mesentery and Peritoneum.* Appendicectomy. Appendix Abscess. Pelvic Abscess. Subphrenic Abscess. Removal of Mesentric Cyst. Paracentesis of Peritoneum. Peritoneoscopy. *Section: V: Spleen, and Operations for Portal Hypertension.* Splenectomy. Splenectomy: Extraperitoneal Mobilization. Portal Hypertension: Measurement, Venography and Oesophageal Haemorrhage Control. Portal Hypertension: Splenosis. Renal Anastomosis. Portal Hypertension: Porta-Caval Anastomi Portal Hypertension: Oesophageal and Gastric Transection. *Section VI: Pancreas.* Exposure of the Pancreas. Pancreato-Duodenectomy. Total Pancreatectomy. Distal Pancreatectomy. Trans-Duodenal Biopsy of Pancreas. Conservative Resections for Tumours Around the Ampulla of Vater. Biliary Short-Circuit for Obstructive Jaundice. Operation

for Hyperinsulinism. Cysts and Cystic Tumour of the Pancreas. Operations for Pancreatic Fistula. Operations for Acute Pancreatitis. Operations for Chronic Relapsing Pancreatitis. *Section VII: Biliary System and Liver.* Partial Hepatectomy. Liver Abscess. Hydatid of Liver. Cholecystostomy. Cholecystectomy. Exploration of the Bile Ducts. Repair of Severed or Strictured Bile Ducts. *Section VIII: Small Intestine.* Jejunostomy. Ileostomy. Neonatal Obstructions. Resection and Anastomosis of the Small Intestine. Ileo-Sigmoidostomy. Ileo-Rectal Anastomosis. Excision of Meckel's Diverticulum. Intussusception. Innocent Tumours and Diverticula. Treatment of External Intestinal Fistulas. *Section IX: Large Bowel.* Sigmoidoscopy. Caecostomy. Colostomy. Closure of Colostomy. Right Hemicolectomy, with Anastomosis. Partial Colectomy, with Anastomosis. Partial Colectomy: Paul. Total Colectomy. Operations for Volvulus of the Large Bowel. Perforated Diverticulitis. Operations for Diverticulitis with and without Vesico-Colic Fistula.

OPERATIVE SURGERY. VOLUME 3

Operative Surgery. Volume 3. *Rectum and Anus, Thorax.* Under the General Editorship of Charles Rob, M.C., M.Chir., F.R.C.S. and Rodney Smith, M.S., F.R.C.S. Pp. xii + 96. (Part IV) + 215 (Part V) + 4 (Index). 464 Illustrations. 1957.

Contents: Part IV: Rectum and Anus. Section I: Diagnostic Procedure. Proctoscopy. *Section II: Non-malignant Conditions.* Injection of Haemorrhoids. Fissure-in-Ano. Rectal Polyp. Haemorrhoidectomy. Fistula-in-Ano. Ischio-Rectal Abscess. Ano-Rectal Atresia with Associated Fistulas. Rectal Prolapse. Rectosigmoidectomy for Hirschsprung's Disease. Excision of Pilonidal Sinus. *Section III: Malignant Conditions.* Combined Excision of the Rectum. Resections with Restoration of Continuity for Rectal Cancer. *Part V: Thorax. Section I: Endoscopy.* Bronchoscopy. Oesophagoscopy. Thoracoscopy and Division of Adhesions. *Section II: Minor Procedures.* Aspiration of Pleural and Pericardial Cavities. Induction of Artificial Pneumothorax. Bronchography. Phrenic Nerve Crush. *Section III: Access.* Surgical Access to the Chest. *Section IV: Operations on the Chest Wall.* Intercoastal Drainage of Empyema. Rib Resection for Empyema. Tumour of Chest wall. Thoracoplasty with Apicolysis. Decortication—Pleurectomy: Excision of Empyema. Extrapleural Pneumonolysis. Extra-periosteal Plombage. *Section V: Operations of the Lungs.* Pneumonectomy. Lobectomy. Segmental Resection of Lung: Removal of Cysts. *Section VI: Heart, Pericardium and Great Blood Vessels.* Open Hear Surgery: Methods of Obtaining Ideal Conditions. Pericardiectomy and Drainage of the Pericardium. Persistent Ductus Arteriosus. Congenital Abnormalities: Tetralogy of Fallot. Congenital Abnormalities: Atrial Septal Defects. Congenital Abnormalities: Coarctation of the Aorta. Congenital Abnormalities: Congenital Abnormalities: Pulmonary Stenosis. Mitral Valvotomy. Pulmonary Embolectomy. Cardiac Arrest—Cardiac Massage and Treatment. *Section VII: Operations on the Mediastinum.* Transthoracic Removal of Tumour or Cyst. Excision of Intrathoracic Goitre. *Section VIII: Oesophagus.* Operations for Carcinoma of the Oesophagus. Operations for Achalasia or Cardiospasm. Congenital Abnormalities of the Oesophagus. Operations for Reflux Oesophagus. Index.

The high standard achieved in Volume One has been maintained and indeed exceeded in Volumes Two and Three of this monumental work on Operative Surgery.

In Volume Two the sections on Hernia, Portal Hypertension, the Biliary System and the Pancreas are excellent. Rodney Smith's contribution on operations for pancreatic disease is a masterpiece. Most of the chapters on the Small Intestine are good but the contribution on Neonatal Obstructions leaves room for improvement. The chapters on the Large Bowel are good.

Volume Three contains a most valuable section on non-malignant conditions of the Rectum and Anus, although the chapters on prolapse could be improved by inclusion of the details of procedures other than rectosigmoidectomy, the results of which leave much to be desired. The chapters on malignant conditions of the rectum are first rate.

Volume Three also contains up-to-date chapters on pulmonary and cardiac surgery by men whose names have become household words in the field of thoracic surgery. Franklin's contributions on the oesophagus are all good although the illustrations could be improved.

Your reviewer found these volumes of inestimable value and has no hesitation in recommending them to all surgeons and particularly to those who do not have the opportunity of doing major surgery on a large scale. The excellence of the work outweighs any theoretical disadvantages that critics may level against this method of learning the essential steps of operative surgery.

J.H.L.

TUMOURS OF THE EYE

Tumors of the Eye and Adnexa. Fascicle 38 of Atlas of Tumor Pathology. By Algernon B. Reese. Pp. 205. With 122 illustrations. Washington: Armed Forces Institute of Pathology. $2.00. 1956.

Contents: Epithelial Tumors of the Eye. Neuroectoderma Tumors. Melanomas. Mesodermal Tumors. Tumors of the Lacrimal Gland. Metastatic Tumors. Orbit Neoplasms and Lesions Simulating them. References.

This book must not be confused with the author's well known and authoritative 'Tumours of the Eye'. It is a completely separate entity, being an atlas of these conditions with the text a secondary consideration, concise and thorough as it is. In fact, there are 70 pages of text (and this includes numerous tables and abundant references). The remainder is composed of extremely beautiful illustrations on excellent art paper of the various tumours to be found in the eye and its adnexa. Each illustration is accompanied by its separate descriptive text. It is for instance clearly demonstrated that rosette formation in retinoblastoma is evidence of a neuro-epitheliomatous type of growth, indicating a slower, less malignant lesion. Retinoblastoma is not a purely local and cranial disease, but disseminates widely by way of the blood stream.

In criticism, it may have been preferable to have had the text and illustrations separate, instead of being interspersed as it is. In the former layout, it would be easier to read the complete text through, instead of having to page over several sheets of illustrations in between sentences. The excellence of the illustrations is distracting! The present layout, however, has the advantage that the illustration accompanies the text to demonstrate the particular point being made.

This book then is a useful addition to the library of the Ophthalmologist and Pathologist, dealing as it does with a limited field in an adequate way.

L.S.

EXCERPTA MEDICA

Excerpta Medica. The International Medical Abstracting Service. Cardiovascular Diseases. Vol. I. No. 1. Section XVIII. January 1957. (Abstr. No. 1—303.) Editor: J. W. C. de Groot. Pp. 78. Each yearly volume will contain 800 to 900 pages inclusive of the yearly authors' index and a cross-referenced subject index. Subscription fee $15 per year. Amsterdam: The Excerpta Medica Foundation. 1957.

Contents: Foreword. Classification. 1. Anatomy, Embryology and Histology of the Circulatory System. 2. Physiology. 3. Diagnostic Procedures. 4. The Heart in Health and Disease. 5. Diseases of Endocardium and Valves. 6. Diseases of Myocardium and Coronary System. 7. Rheumatic Heart Diseases. 8. Disturbances of Pulse Rate and Cardiac Rhythm. 9. Diseases of the Pericardium. 10. Medical Treatment of Cardiac Diseases. 11. The Rehabilitation of the Cardiac Patient and His Social Problems. 12. Abnormalities of the Systemic Circulation. 13. The Pulmonary Vascular Bed. 14. Vascular Diseases. 15. Congenital Cardiovascular Diseases. 16. Cardiovascular Tumours. 17. Surgical Treatment (Cardiovascular Surgery). 18. Experimental Medicine and Surgery. 19. Anaesthesia and Supportive Measures in Cardiovascular Diseases.

In this volume there are 303 short extracts from current journals of the World literature. The various sections of cardiovascular disease are covered.

R.S.T.

LYSERGIC ACID DIETHYLAMIDE

Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry. Edited by Louis Cholden, M.D. Pp. xi + 85. $3.00. New York and London: Grune & Stratton Inc. 1956.

Contents: Introduction—Louis Cholden. Panel Discussion: Pharmacology of LSD-25—E. Rothlin and A. Cerletti, Studies in Routes of Administration and Counteracting Drugs—Paul H. Hoch. Biochemical Reflections on the Psychosis Problem—Max Rinkel. The Effect of Frenquel on EEG Changes Produced by LSD and Mescaling—Harold E. Himwich. The Clinical Uses of LSD—R. A. Sandison, The LSD Psychosis as a Transaction between the Psychiatrist and Patient—Charles Savage, Studies with Niacin and LSD—A. Hoffer, Mescaline and the 'Other World'—Aldous Huxley, Some Observations on Normal Volunteers and Patient—Harold A. Abramson, Brain Effects of LSD in Animals—Edward Evarts, Preliminary Studies on the Metabolism of LSD—Eugene S. Boyd, Summary and Discussion—Harry Pennes. Questions and Discussion—the Audience. Answers and Final Statements—the Panel. Index.

In May 1955, the American Psychiatric Association held a symposium on lysergic acid diethylamide (LSD) and mescaline. The little book under review consists of a presentation of the papers which various workers doing psychiatric research with these drugs read at that meeting.

It has been discovered that LSD and mescaline can be used to induce a schizophrenic-like psychosis and this has suggested the possibility that a pharmacological approach to schizophrenia might ultimately lead to the solving of some of the mysteries of this dread mental reaction. In this short collection of papers, one finds LSD and mescaline induced psychoses fully described, as well as accounts of the findings of other experimental work pertaining to the subject. There is also a very interesting report

on the use of these drugs in the management of neurotic states. Under the influence of these drugs, neurotic patients readily released formerly repressed, unconscious psychologically traumatic experiences.

These reports leave the reader with the realization that the research being done in this field is as yet in its infancy. At this stage, conclusions to be drawn from the findings are nebulous in the extreme, but one is left with no doubt that this pharmacological approach to psychological disorders warrants further investigation. Those interested in the research which is being done in this field of psychiatry will find this book stimulating.

H.C.

ENDEMIC SYPHILIS

Endemic Syphilis in the Bakwena Reserve of the Bechuanaland Protectorate. By J. F. Murray, M.B., Ch.B., M.D., D.P.H., A. M. Merriweather, M.B., Ch.B., D.T.M. & H., M.R.C.P., M. L. Freedman, O.B.E., M.B., Ch.B., D.P.H. with D. J. de Villiers. Pp. 975-1039. 76 Illustrations. Geneva: World Health Organization. 1956.

Contents: Synopsis. Notes on the Bakwena Reserve. Topography. Ethnology. History. Purpose of the Investigation. Organization of the Field Campaign. Difficulties encountered. Villages and number seen. Epidemiological Considerations. A disease of low hygienic standards. A family disease. Course and Clinical Features of Dichuchwa. Summary of cases and analysis of clinical findings. TPI test. Relationship of Dichuchwa to Witkop. Relationship of Dichuchwa to Other Treponematoses. Summary of the Relationships of the Treponematoses. Treatment of Dichuchwa with Penicillin. Acknowledgements Resume. References.

Much credit is due to the various organizations that encouraged and financed the medical expedition which made a survey of endemic syphilis in the Bechuanaland Protectorate, that large and sparsely populated territory which lies to the north-west of the Union of South Africa. The investigation was beset with many difficulties. The roads are very bad, or non-existent; there is a great scarcity of water. Communications between communities are very poor and the population so scattered and migratory in their habits. The team are therefore to be highly commended for carrying out their task under such trying circumstances and recording their findings in this bulletin.

In the Bakwena Reserve, home of the tribe of that name, the authors encountered many cases of endemic syphilis, that is, syphilis acquired and spread by non-sexual means. This is made possible by the very low standards of hygiene and unclean habits which obtain in the natives of these parts. The disease is almost identical with syphilis, as we meet it, and is known locally as 'dichuchwa', a word which recalls the Xosa name for syphilis—Ngushuwa. Endemic syphilis is found elsewhere in the world, in Southern Rhodesia, amongst certain Arab tribes and even in some remote communities in South East Europe. It is unlikely that it occurs to any large extent in the Union, though familial outbreaks of syphilis are seen from time to time.

This small volume is a special bulletin of World Health Organization presenting the report of a survey of endemic syphilis in the Bechuanaland Protectorate. The general climatic, social and economic background of the inhabitants is first outlined and a brief sketch of the plan of campaign is given. The fact that no less than 35,043 cases were examined and blood specimens taken from them gives some idea of the magnitude of the task and the efficiency of the organization that made this possible. The percentage of positive Wassermann reactors in this huge total was 37·0. It was higher in Kalahari villages than elsewhere; in one particular village the astounding figure of 72·0% was revealed.

The authors discuss the relation between the various manifestations of Treponematosis—classical syphilis, dichuchwa, Jebel (Arab syphilis), yaws and pinta. Under ordinary microscopic examination no differences can be made out between the treponemes found in all these conditions. Dichuchwa, although principally conveyed by non-sexual means, can, as the authors observed, be acquired sexually. Classical syphilis is broadly distinguishable from the other diseases by the occurrence of central nervous system involvement and by its characteristic association with cardio-vascular complications and congenital transmission.

Numerous cases of Witkop were seen and the aetiology of this strange condition is fully discussed. Is it due to syphilis? Is it a fungus infection? Though the authors incline to the second diagnosis some doubt still exists. There are very good descriptions of the many clinical forms of 'dichuchwa'. Here and there terms and phrases are used which sound somewhat quaint. For instance a rash is described as 'papilliform' and lymph glands are referred to as 'ganglia'. French writers use the word 'ganglion' when referring to a lymph gland but in English it usually means a collection of nerve tissue or a tumour along the course of a muscle tendon. In remarking on the rarity of primary lesions the text states: 'When syphilis is acquired venereally the mucous membranes are heavily inoculated by treponemes and a primary sore develops'. This is scarcely a happy choice of words to describe the phenomenon of the chancre reaction in syphilis. Nor can the short dissertation on superinfection be described as a useful or decisive contribution to this still debatable point. But these are minor, superficial criticisms prompted, possibly, by the tendency every reviewer has to find fault somewhere.

Every aspect of their problem received the closest and expert attention of the investigators. And it speaks well for the thoroughness and care with which the expedition was planned that selected specimens of blood were sent by air to the Danish State Serum Institute for testing by the Treponema Immobilization Test and innoculated hamsters to the Johns Hopkins Hospital in Baltimore for special study of the strain of Treponema pallidum causing dichuchwa.

The statistical data obtained by the investigation are contained in thirteen well arranged, informative tables. Some idea can be gained of the scope of the survey by learning from Table 8 that 22,809 persons were interviewed, had specimens of their blood examined by the VDRL and Kolmer cardiolipin complement fixation tests, and the results presented under 44 different headings! All the more surprising therefore is it to find on page 1027 (the report is paged from 975 to 1039) a treatment schedule which merely gives a series of figures 0·3, 0·6, 0·9, 0·18 etc. without any indication of what these figures mean. From the context one assumes that they stand for millions of units of PAM; but the lack of any explanatory note of their significance is such a carefully documented report is striking. The illustrations at the end of the report are excellent. They are photographs in black and white of some of the cases seen by the team and they vividly portray the destruction and disabilities caused by endemic, untreated syphilis amongst these unfortunates.

It is gratifying to learn that the labours and physical discomforts borne by the three authors and their team of helpers initiated a campaign of general social and hygienic improvement combined with a mass therapy scheme which has already produced a lessening in the incidence of dichuchwa. They confidently express the opinion that such a programme if maintained would eliminate dichuchwa in a relatively short time. Everyone will join them in hoping that this will come to pass. But it is difficult to follow the train of thought that leads them to express the fear that once endemic syphilis is eradicated, classical, venereal syphilis will enter in its place. For when all is said and done dichuchwa is syphilis modified by the habits of the Bechuana tribes and is just as susceptible to penicillin as venereal syphilis. That being so, provided treatment services are retained, its gradual elimination, or, at least suppression, is only a matter of time.

C.K.O'M.

ANNUAL EPIDEMIOLOGICAL AND VITAL STATISTICS

Annual Epidemiological and Vital Statistics, 1954. World Health Organization, Geneva, 1957, 617 pages. Price £2 10s., $10.00, Fr. frs. 2,400 or Sw. fr. 30. Bilingual edition (French and English). Local Sales Agent: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724, Pretoria.

The vital statistics and state of health of the world in 1954 are reflected in more than 580 pages of figures, collected in 109 tables. Through these conventional symbols, the figures, it is possible to give a picture of the population of each country, its growth and the illnesses from which it suffers, as well as of the extreme diversity of the conditions that exist—in short, to show what it is that the inhabitants of any part of the globe suffer and die from.

In addition to the usual sections on population and vital statistics, causes of death and cases of communicable disease, this new edition of the WHO year book contains a new part dealing with health personnel, the number and distribution of hospitals

and the vaccinations of various types carried out in each country.

The year book is planned to fulfil a double purpose: (1) to supply basic documentation in the form of actual official figures, thus avoiding the need for long and sometimes futile searches (since part of this documentation is, in fact, unpublished, being communicated to WHO through special questionnaires); (2) to facilitate the immediate understanding of the data by a collection of specific mortality rates, referring, for example, to a group of countries, to some particular cause of death for a given age and sex. Particularly detailed information is given on tuberculosis, cancer, cardiovascular diseases, etc. A new table gives death rates by sex and age for the infective and parasitic diseases as a whole in 24 countries. These figures are remarkable, for they reveal how greatly health conditions vary in different parts of the world, so that the mortality from infective disease among infants may be twenty times higher in one country than it is in another. Study of the other tables shows why this is so.

SNAIL ECOLOGY IN BILHARZIA

Study Group on the Ecology of Intermediate Snail Hosts of Bilharziasis: Report. *World Health Organization: Technical Report Series*, 1957, No. 120, 38 pages. Price 1s. 9d., $0.30, Sw. fr. 1. Also available in French and Spanish. Local Sales Agent: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724, Pretoria.

The increased incidence of bilharziasis during the last years has stimulated research for practical control measures. Destruction of the intermediate host would appear to be a logical line of approach, but it has become apparent, in part indeed from the limited success of snail control, that comparatively little is known about the relationship between the ecology of the snails and the mechanism of infection.

In this report, the distribution of intermediate snails hosts in relation to hydrogeology and the factors conditioning the habitat and breeding conditions are discussed. It is pointed out that snails are able to withstand for a considerable period of time temperatures ranging from a little above freezing point to well above 37°C. The effect of light and of currents in the water on snail populations receive special attention. If it were proved that light had an indispensable stimulating action on the sex glands of the snails, covering the irrigation channels or piping the irrigation water could be considered as a practical method of control. Dessication, on the other hand, on account of the resistance shown by a proportion of the snails can only be effective under special conditions.

Seasonal and climatic factors influencing the life cycle of the snail and the present knowledge of ecology and its application to bilharziasis control measures are then examined. The report states that much remains to be learned about the complex relationships existing between molluscicides, the snails and the environment. Fishing and farming practices in some places have a profound effect on the occurrence of intermediate snail hosts. In a control experiment carried out in the Pacific region, the density of the snail population was greatly reduced by modifying rice-growing practices, and this fact is of importance as a practical measure of control.

Finally, quantitative methods for the measurement of the density of mollusc populations and for the evaluation of results of control methods are indicated.

'The development of ecological research has now reached a point at which extensive field studies can no longer be efficiently carried out by individuals, and cooperation between specialists in different scientific disciplines is desirable.'

MODERN MEDICINE FOR NURSES

Modern Medicine for Nurses. 4th Edition. By Patria Asher, M.D., M.R.C.P. Pp. xiii + 378. Figs. 99. 22s. 6d. net. London: William Heinemann Medical Books Ltd. 1957.

Contents: Preface to the Fourth Edition. *Part I.—General Principles.* I. Rest. II. Food. III. Record Keeping (*a*) The Temperature Chart. IV. Record Keeping (*b*) Pulse and Respiration Rates. V. Urine Testing. VI. Bowel Action. VII. The Control of Cross Infection. VIII. General Ward Management. *Part II.—Common Diseases and their Treatment.* IX. Diseases of the Heart and Blood Vessels. X. Diseases of the Chest. XI. Diseases of the Blood, Spleen and Lymph Glands. XII. Digestive Disorders. XIII. Urinary Diseases. XIV. Diseases of Joints and Muscles. XV. Endocrine Disorders. XVI. Diabetis Mellitus. XVII. Skin Diseases. XVIII. Diseases of the Nervous System. XIX. Infestions and Infestations. XX. Diseases of the Nose, Mouth and Throat. XXI. Children's Diseases. XXII. The Social Aspects of Disease. XXIII. Mental Ill-Health (by Portia Holman). Appendix (*a*) Some Practical Procedures. Appendix (*b*) Pharmaceutical terms and Tables of Weights and Measures. Glossary. Index.

It was in 1954 that I had the pleasure of reading the third edition of this book for review.

Its worth and value must be realised by nurses in many countries, and the fourth edition is now available. The text shows many evidences of having been fully revised, and indeed some portions have been re-written. In addition there are new sections on pulmonary collapse, ankylosing spondylitis, the nursing of the unconscious patient, and the uses of cortisone and allied drugs.

There is little doubt that the nurse who has studied this book carefully will have a sound knowledge of the subject and should have little difficulty in satisfying her examiners.

A.H.T.

CORRESPONDENCE : BRIEWERUBRIEK

RECENT ADVANCES CONCERNING HYPERPARATHYROIDISM

To the Editor: Your otherwise accurate leading article under this title[1] which appeared in the *Journal* of 5 October, carries two assertions which I feel should be challenged.

The first, which is clearly implied, states that hyperparathyroidism can be excluded by the finding of a normal urine-calcium output, and hence the simple test with Sulkowitch's reagent serves as an adequate screening test for this disease. Workers with considerable experience of the condition[2,3] have found that the 24-hourly urine-calcium excretion is by no means invariably raised in this disease, and may fall to low levels when renal failure supervenes. In addition, Sulkowitch's test is a semi-quantitative test for urine calcium *concentration* and, as the very nature of the nephropathy of hyperparathyroidism (Calcinosis of the distal tubule) is such that it will produce copious quantities of dilute urine, it is easy to conceive of cases being missed if too much reliance is placed upon this test.

The second assertion which needs qualification is that direct measurement, using phosphate and inulin infusions, of the phosphate Tm can be of use in difficult cases. It is the belief of Professor Dent[4] (and in this he has my strong support) that these complicated measures are unnecessary when the serum phosphorus is low, and valueless when it is normal or elevated. This is scarcely surprising if one assumes that the serum-phosphorus level in hyperparathyroidism is regulated by renal tubular activity and is, in itself, a measure of this activity.

With knowledge in its present state, the clinical approach to cases of suspected hyperparathyroidism is not a question of 'diagnose or exclude'. It involves a very nice decision as to when to explore the parathyroids and when not to. It is doubtful if the more elaborate tests described in your leading article will help in the making of this decision more than observation over a period of time of the clinical status and the concentrations of calcium, phosphorus and urea in the serum.

E. B. D. Dowdle
Medical Registrar to Prof. G. M. Bull

Department of Medicine
Institute of Clinical Science
Queen's University of Belfast
Belfast, Northern Ireland
31 October 1957

1. Editorial (1957): S. Afr. Med. J., **31**, 1003.
2. McGeown, M. (1957): Personal communication.
3. Fraser, R. (1957): Personal communication.
4. Dent, C. E. (1956): Brit. Med. J., **1**, 230.